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(54) Title: PHARMACEUTICALLY USEFUL COMPOUNDS

(57) Abstract

The invention relates to 2-arylpyrazolisoquinoline and cinnolinone derivatives, methods for their preparation, their use as medicaments, and pharmaceutical formulations including them.

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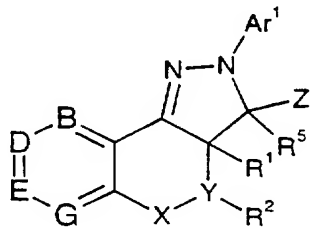
PHARMACEUTICALLY USEFUL COMPOUNDS

This invention relates to pharmaceutically useful compounds, methods for their preparation, their use as medicaments, and pharmaceutical formulations including them.

Certain pyrazolo[4,3-*c*]isoquinolin-3-ones are known from *J. Chem. Soc.* 599 (1959) (Hinton *et al.*). Their use as pharmaceuticals is not suggested. The synthesis and ability of certain pyrazolo[4,3-*c*]isoquinolin-3-ols to inhibit radioligand binding to benzodiazepine receptors has been detailed in *J. Med. Chem.* **35**, 368 (1992) (Allen *et al.*). Certain other pyrazolo[4,3-*c*]isoquinolin-3-ols are disclosed in *Gaodeng Xuexiao Huaxue Xuebao* 1991, **12**, 1620–1622 (Qian Jian-hua *et al.*). No pharmaceutical use of the compounds in question is mentioned.

It has now been found that 2-arylpyrazolisoquinoline and cinnolinone derivatives exhibit anti-allergic and anti-inflammatory activity. In a first aspect the invention therefore provides a compound of formula I or a pharmaceutically acceptable derivative thereof for use as a pharmaceutical:



(I)

wherein:

- B, D, E and G each represent CH, CA or N provided that no more than one of B, D, E and G represents CA and no more than one of B, D, E and G represents N;
- X represents C=O, C=S, C=NR^{15}, CR^{3}R^6 or NR^4;
- Y represents N or N$^+$R^7 or CR^{18};
- Z represents OR^8 or O$^-$;
- R^1 represents OH or C_{1-6} alkyl, or with either R^2 or R^5 forms a bond;
- R^2 represents H, C_{1-6} alkyl (optionally substituted by phenyl, COOR^9, NR^{10}R^{11}, OR^{12} or F) or C_{3-7} cycloalkyl, or with either R^1, R^3 or R^4 forms a bond;
- R^3 represents H or a bond with R^2;
- R^4 represents C_{1-6} alkyl or a bond with R^2;

- R^5 represents a bond with R^1 or R^8;
- R^6 represents H, C_{1-6} alkyl (optionally substituted by phenyl), C_{3-7} cycloalkyl, phenyl, halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, cyano or $NR^{13}R^{14}$;
- R^7 represents C_{1-6} alkyl (optionally substituted by phenyl) or C_{3-7} cycloalkyl, either of which may be optionally substituted by halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, $NR^{16}R^{17}$, COOH, $COO(C_{1-6}$ alkyl) or cyano;
- or R^6 and R^7 together represent C_{3-5} alkylene, X and Y thereby forming a ring of 5–7 members;
- R^8 represents H, C_{1-6} alkyl or a bond with R^5;
- R^9, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17} and R^{18} independently represent C_{1-6} alkyl or H;
- R^{13} and R^{14} are independently C_{1-6} alkyl, H or together with the nitrogen atom to which they are attached form a 3-7 membered saturated ring optionally containing a further oxygen atom or a nitrogen atom optionally substituted by C_{1-6} alkyl;
- Ar^1 represents phenyl, pyridyl, pyrimidinyl, 2-benzothiazolyl, 2- or 3-quinolyl or 2-quinoxalinyl, all of which are optionally substituted by one or more substituents selected from halo, nitro, cyano, phenyl, phenylsulfonyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, COOH, $COO(C_{1-6}$ alkyl), C_{1-6} alkyl substituted by phenyl, or phenyl, in which any alkyl, alkoxy, alkylthio and alkylsulfinyl groups may optionally be substituted by fluoro; and
- A represents halo, cyano, amino, nitro, C_{1-6} alkyl or C_{1-6} alkoxy;

in which phenyl groups which are found in R^2, R^6, R^7 or as substituents on Ar^1 may be optionally substituted by C_{1-6} alkyl, halogen or C_{1-6} alkoxy;

with the provisos that:

(i) when X represents C=O, C=S or $C=NR^{15}$, then Y represents N;

(ii) when R^4 represents a bond with R^2, then Y represents N^+R^7;

(iii) when Y represents N^+R^7, then Z represents O^-, R^2 represents a bond with R^3 or R^4 and R^1 and R^5 form a bond;

(iv) when Y represents N, then Z represents OR^8;

(v) when R^1 represents OH, then X represents C=O, Y represents N, Z represents OR^8 and R^5 represents a bond with R^8;

(vi) when R^1 represents alkyl, then R^5 represents a bond with R^8, Y represents N, R^2 does not represent a bond, and X does not represent NR^4;

(vii) when R^1 represents a bond with R^2, then R^5 and R^8 form a bond, and if X represents NR^4 then R^4 represents alkyl;

(viii) when R^6 represents aryl, halogen, alkoxy, thioalkyl, then R^2 and R^3 form a bond;

(ix) when Y represents N or N^+R^7 and R^2 is substituted by any of $NR^{10}R^{11}$, OR^{12} or F, then the substituent and the ring nitrogen of Y may not be attached to the same carbon atom of R^2;

(x) when R^7 is substituted by any of $NR^{16}R^{17}$, OR^{12} or halogen then the substituent and the ring nitrogen of Y may not be attached to the same carbon atom of R^7;

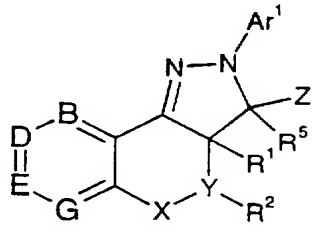
(xi) when one of B, D, E and G represents N, then X does not represent NR^4;

(xii) when Y represents CR^{18}, then X represents CR^3R^6;

with the further proviso that:

- when B, D, E and G all represent CH, X represents CHR^3, Y represents nitrogen, R^1 and R^5 form a bond, R^8 represents H and R^2 and R^3 together represent a bond, then Ar^1 does not represent unsubstituted phenyl, 4-chlorophenyl, 4-fluorophenyl or 4-methoxyphenyl.

Certain compounds of formula (I) are novel. According to the invention there is further provided a compound of formula I:



(I)

wherein:

- B, D, E and G each represent CH, CA or N provided that no more than one of B, D, E and G represents CA and no more than one of B, D, E and G represents N;
- X represents C=O, C=S, $C=NR^{15}$, CR^3R^6 or NR^4;
- Y represents N or N^+R^7 or CR^{18};
- Z represents OR^8 or O^-;
- R^1 represents OH or C_{1-6} alkyl, or with either R^2 or R^5 forms a bond;
- R^2 represents H, C_{1-6} alkyl (optionally substituted by phenyl, $COOR^9$, $NR^{10}R^{11}$, OR^{12} or F) or C_{3-7} cycloalkyl, or with either R^1, R^3 or R^4 forms a bond;
- R^3 represents H or a bond with R^2;
- R^4 represents C_{1-6} alkyl or a bond with R^2;
- R^5 represents a bond with R^1 or R^8;

- R^6 represents H, C_{1-6} alkyl (optionally substituted by phenyl), C_{3-7} cycloalkyl, phenyl, halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, cyano or $NR^{13}R^{14}$;
- R^7 represents C_{1-6} alkyl (optionally substituted by phenyl) or C_{3-7} cycloalkyl, either of which may be optionally substituted by halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, $NR^{16}R^{17}$, COOH, $COO(C_{1-6}$ alkyl) or cyano;
- or R^6 and R^7 together represent C_{3-5} alkylene, X and Y thereby forming a ring of 5–7 members;
- R^8 represents H, C_{1-6} alkyl or a bond with R^5;
- R^9, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17} and R^{18} independently represent C_{1-6} alkyl or H;
- R^{13} and R^{14} are independently C_{1-6} alkyl, H or together with the nitrogen atom to which they are attached form a 3-7 membered saturated ring optionally containing a further oxygen atom or a nitrogen atom optionally substituted by C_{1-6} alkyl;
- Ar^1 represents phenyl, pyridyl, pyrimidinyl, 2-benzothiazolyl, 2- or 3-quinolyl or 2-quinoxalinyl, all of which are optionally substituted by one or more substituents selected from halo, nitro, cyano, phenyl, phenylsulfonyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, COOH, $COO(C_{1-6}$ alkyl), C_{1-6} alkyl substituted by phenyl, or phenyl, in which any alkyl, alkoxy, alkylthio and alkylsulfinyl groups may optionally be substituted by fluoro; and
- A represents halo, cyano, amino, nitro, C_{1-6} alkyl or C_{1-6} alkoxy;

in which phenyl groups which are found in R^2, R^6, R^7 or as substituents on Ar^1 may be optionally substituted by C_{1-6} alkyl, halogen or C_{1-6} alkoxy;

with the provisos that—

(i) when X represents C=O, C=S or $C=NR^{15}$, then Y represents N;

(ii) when R^4 represents a bond with R^2, then Y represents N^+R^7;

(iii) when Y represents N^+R^7, then Z represents O^-, R^2 represents a bond with R^3 or R^4 and R^1 and R^5 form a bond;

(iv) when Y represents N, then Z represents OR^8;

(v) when R^1 represents OH, then X represents C=O, Y represents N, Z represents OR^8 and R^5 represents a bond with R^8;

(vi) when R^1 represents alkyl, then R^5 represents a bond with R^8, Y represents N, R^2 does not represent a bond, and X does not represent NR^4;

(vii) when R^1 represents a bond with R^2, then R^5 and R^8 form a bond, and if X represents NR^4 then R^4 represents alkyl;

(viii) when R^6 represents aryl, halogen, alkoxy, thioalkyl, then R^2 and R^3 form a bond;

(ix) when Y represents N or N^+R^7 and R^2 is substituted by any of $NR^{10}R^{11}$, OR^{12} or F, then the substituent and the ring nitrogen of Y may not be attached to the same carbon atom of R^2;

(x) when R^7 is substituted by any of $NR^{16}R^{17}$, OR^{12} or halogen then the substituent and the ring nitrogen of Y may not be attached to the same carbon atom of R^7;

(xi) when one of B, D, E and G represents N, then X does not represent NR^4;

(xii) when Y represents CR^{18}, then X represents CR^3R^6;

with the further provisos that:

(a) when B, D, E and G all represent CH, X represents CHR^3, Y represents N, R^1 and R^5 form a bond, R^8 represents H and R^2 and R^3 together represent a bond, then Ar^1 does not represent unsubstituted phenyl, 4-chlorophenyl, 4-fluorophenyl or 4-methoxyphenyl;

(b) when B, D, E and G all represent CH, X represents CHR^3, Y represents N^+R^7, R^1 and R^5 form a bond, R^2 and R^3 represents a bond, R^8 represents H, and R^7 represents methyl, then Ar^1 does not represent unsubstituted phenyl;

(c) when B, D, E and G all represent CH, X represents CH_2, Y represents N, R^1 and R^5 form a bond, R^8 represents H, and R^2 represents isopropyl, then Ar^1 does not represent unsubstituted phenyl or 4-bromophenyl; and

(d) when B, D, E and G all represent CH, X and Y represent CH_2 and R^1 and R^5 form a bond, then Ar^1 does not represent unsubstituted phenyl.

or a pharmaceutically acceptable derivative thereof.

Preferably Ar^1 represents phenyl or pyridyl, most preferably phenyl. The phenyl group Ar^1 preferably has a substituent in the *para* position, more preferably a Cl, Br, CF_3, C_2F_5, OCF_3 or SCH_3 substituent in the *para* position especially a CF_3, C_2F_5, OCF_3 or SCH_3 substituent in the *para* position.

Preferably Y represents N^+R^7, and X represents CR^3R^6 in which R^3 forms a bond with R^2 and R^6 represents alkyl. In such a case, R^6 preferably represents branched alkyl. Alternatively, X may represent NR^4 in which R^4 represents a bond with R^2 and Y represent N^+R^7.

Preferably B represents CA. In such a case, A preferably represents F.

In the case where one of B, D, E and G represents N, preferably it is D or G that represents N.

Preferably R^1 represents a bond with R^2 or R^5. In such a case, R^1 preferably represents a bond with R^5.

Particularly preferred compounds of the invention include those exemplified herein including the free form and all salts and solvates thereof.

Pharmaceutically acceptable derivatives includes solvates and salts. Particular salts which may be mentioned include hydrochloride, hydrobromide, benzenesulfonate, tosylate and methanesulfonate.

The compounds of formula I may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention. The compounds of formula I may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. All diastereoisomers may be separated using conventional techniques, for example chromatography or fractional crystallisation. The various optical isomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, for example fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (for example HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

Alkyl groups which R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} may represent or which may be substituted on one or more of the aromatic rings forming part of Ar^1 may be saturated or unsaturated, and straight chain or branched. C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, $COO(C_{1-6}$ alkyl) and C_{3-5} alkylene are to be interpreted accordingly.

According to the invention there is also provided a process for the preparation of compounds of formula I which comprises:

(a) preparation of compounds of formula I where X represents CH_2 or C=O, Y represents N, Z represents OR^8, R^5 and R^8 form a bond and R^1 and R^2 form a bond by oxidation of a corresponding compound of formula I where R^1 and R^2 both represent H and B, D, E, G, X, Y, Z, Ar^1 and R^5 are as hereinbefore defined, for example at room

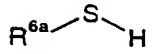
temperature using a suitable oxidising agent (for example manganese dioxide) and an appropriate organic solvent;

(b) preparation of compounds of formula I where one of B, D, E and G represents CA wherein A represents amino by reduction of a corresponding compound of formula I, where one of B, D, E and G represents CA wherein A represents nitro and the remainder of B, D, E and G, and X, Y, Z, Ar^1, R^1, R^2 and R^5, are as hereinbefore defined, for example with iron powder and ammonium chloride in refluxing ethanol;

(c) preparation of compounds of formula I where one of B, D, E and G represents CA wherein A represents halo by diazotisation of a corresponding compound of formula I, where one of B, D, E and G represents CA wherein A represents amino and the remainder of B, D, E and G, and X, Y, Z, Ar^1, R^1, R^2 and R^5, are as hereinbefore defined, and decomposition of the diazonium salt in the presence of the halide anion or (for fluorine) sodium tetrafluoroborate in dichlorobenzene at reflux;

(d) preparation of compounds of formula I where one of B, D, E and G represents CA wherein A represents cyano by reaction of a corresponding compound of formula I, where one of B, D, E and G represents CA wherein A represents bromo and the remainder of B, D, E and G, and X, Y, Z, Ar^1, R^1, R^2 and R^5, are as hereinbefore defined, by reaction with copper(I) cyanide, for example at reflux in *N*-methylpyrrolidone;

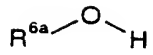
(e) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents alkylthio by displacement reaction of a corresponding compound of formula I, where X represents CR^3R^6 wherein R^6 represents methylthio or halogen and B, D, E, G, Y, Z, Ar^1, R^1, R^2, R^3 and R^5 are as hereinbefore defined, with a compound of formula II:



(II)

wherein R^{6a} represents C_{1-6} alkyl, in the presence of a base, for example sodium hydride, in an appropriate solvent, for example DMF;

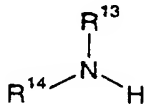
(f) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents alkoxy by displacement reaction of a corresponding compound of formula I, where X represents CR^3R^6 wherein R^6 represents methylthio or halogen and B, D, E, G, Y, Z, Ar^1, R^1, R^2, R^3 and R^5 are as hereinbefore defined, with a compound of formula III:



(III)

wherein R^{6a} is as hereinbefore defined, in the presence of a base, for example sodium hydride, in an appropriate solvent, for example, DMF;

(g) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents $NR^{13}R^{14}$ by displacement reaction of a corresponding compound of formula I, where X represents CR^3R^6 wherein R^6 represents methylthio or halogen and B, D, E, G, Y, Z, Ar^1, R^1, R^2, R^3 and R^5 are as hereinbefore defined, with a compound of formula IV:



(IV)

wherein R^{13} and R^{14} are as hereinbefore defined, in the presence of a base, for example sodium hydrogen carbonate, in an appropriate solvent, for example, DMF at 100 °C;

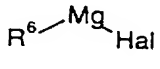
(h) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents methylthio by reaction of a corresponding compound of formula I, where X represents C=S, Y represents N, Z represents OH and B, D, E, G, Ar^1, R^1, R^2, and R^5 are as hereinbefore defined, with a methylating agent, for example, methyl iodide, for example neat at reflux;

(i) preparation of compounds of formula I where X represents C=S, Y represents N, Z represents OH and R^1 represents a bond with R^5 by reaction of a corresponding compound of formula I, where X represents C=O and B, D, E, G, Y, Z, Ar^1, R^1, R^2, and R^5 are as hereinbefore defined, by thionation, for example using Lawesson's reagent in an appropriate solvent, for example dioxane at reflux;

(j) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^- and R^6 represents halogen by reaction of a corresponding compound of formula I, where X represents C=O, Y represents N, Z represents OR^8, R^8 represents a bond with R^5 and B, D, E, G, Ar^1, R^1 and R^2 are as hereinbefore defined, by halogenation, for example with a phosphorus oxyhalide, for example neat at 100 °C;

(k) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents alkyl by reaction of a corresponding compound of formula I, where X represents C=O, Y represents N, Z represents OH, R^1 represents a bond with R^5, B, D,

E, G, and Ar^1 are as hereinbefore defined and R^2 represents a group corresponding to R^7 as hereinbefore defined, by reaction with a nucleophilic alkylating reagent, for example a compound of formula V:



(V)

wherein R^6 is as hereinbefore defined and Hal represents halogen, for example in the presence of a copper salt, for example copper(I) bromide in an appropriate solvent, for example dimethoxyethane, for example at reflux;

(l) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents alkyl by reaction of a corresponding compound of formula I, where X represents CR^3R^6 wherein R^6 represents H and B, D, E, G, Y, Z, Ar^1, R^1, R^2, and R^5 are as hereinbefore defined, with a nucleophilic alkylating reagent, for example a compound of formula V as hereinbefore defined in an appropriate solvent, for example THF, for example at 0 °C;

(m) preparation of compounds of formula I where X represents C=O, Y represents N, Z represents OR^8, R^1 represents a bond with R^5, and R^8 represents alkyl by reaction of a corresponding compound of formula I, where Z represents OR^8 wherein R^8 represents H and B, D, E, G, X, Y, Ar^1, R^1, R^2, and R^5 are as hereinbefore defined, with a compound of formula VI:

R^8Hal (VI)

wherein R^8 and Hal are as hereinbefore defined, for example in the presence of a base, for example sodium hydride, in an appropriate solvent, for example DMF;

(n) preparation of compounds of formula I where R^1 represents OH, X represents C=O, Y represents N, Z represents OR^8 and R^5 represents a bond with R^8 by reaction of a corresponding compound of formula I, where Z represents O^-, R^1 and R^5 form a bond and B, D, E, G, X, Y, Ar^1 and R^2 are as hereinbefore defined, by treatment with an oxidising agent, for example ceric ammonium nitrate, in an appropriate solvent, for example acetonitrile, for example at ambient temperature;

(o) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond and R^1 and R^5 form a bond by reaction of a corresponding compound of formula I, where Y represents N, Z represents OH

and B, D, E, G, X, Ar^1, R^1, R^2, and R^5 are as hereinbefore defined, with a compound of formula IX:

$$R^7Hal \qquad (IX)$$

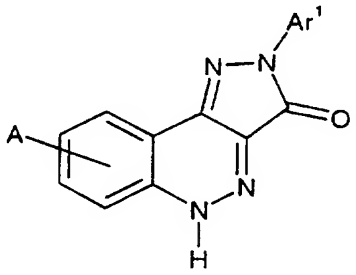
wherein R^7 and Hal are as hereinbefore defined and a base, for example sodium hydride, in an appropriate solvent, for example DMF, for example at ambient temperature;

(p) preparation of compounds of formula I where X represents C=O, R^2 does not represent H, Y represents N, Z represents OH and R^1 represents a bond with R^5 by reaction of a corresponding compound of formula I, where R^2 represents H and B, D, E, G, X, Y, Z, Ar^1, R^1 and R^5 are as hereinbefore defined, with a base, for example sodium hydride, and a compound of formula VII:

$$R^2Hal \qquad (VII)$$

wherein R^2, not representing H, and Hal are as hereinbefore defined, in an appropriate solvent, for example DMF, for example at ambient temperature;

(q) preparation of compounds of formula I where B, D, E and G represent CH or CA, X represents NR^4, Y represents N^+R^7, Z represents O^-, R^4 and R^2 form a bond and R^1 and R^5 form a bond by reaction of a compound of formula VIII:



(VIII)

wherein A and Ar^1 are as hereinbefore defined, with a base, for example sodium hydride, and a compound of formula IX as hereinbefore defined, in an appropriate solvent, for example DMF, for example at ambient temperature;

(r) preparation of compounds of formula I where B, D, E and G represent CH or CA, X represents NR^4, Y represents N, Z represents OR^8, R^2 and R^1 form a bond and R^5 and R^8 form a bond by reaction of a compound of formula VIII as hereinbefore defined with a base, for example sodium hydride, and a compound of formula X:

R^4Hal (X)

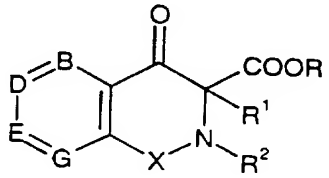
wherein R^4 and Hal are as hereinbefore defined, in an appropriate solvent, for example DMF, for example at ambient temperature;

(s) preparation of compounds of formula I where X represents CR^3R^6, Y represents N, Z represents OH, R^3 and R^2 form a bond and R^1 represents a bond with R^5 by treatment of a corresponding compound of formula I, where Y represents N^+R^7, Z represents O^-, R^7 represents $CH_2C_6H_4Oalkyl$ and B, D, E, G, X, Ar^1, R^1, R^2, and R^5 are as hereinbefore defined, with an acid, for example trifluoroacetic acid, for example at reflux;

(t) preparation of compounds of formula I where X represents CR^3R^6, Y represents N, Z represents OH, R^3 and R^2 form a bond and R^1 represents a bond with R^5 by treatment of a corresponding compound of formula I, where Y represents N^+R^7, Z represents O^-, R^7 represents CH_2phenyl (optionally substituted by C_{1-6} alkyl or C_{1-6} alkoxy) and B, D, E, G, X, Ar^1, R^1, R^2, and R^5 are as hereinbefore defined, with hydrogen in the presence of a catalyst, for example palladium on carbon;

(u) preparation of compounds of formula I where X represents C=O, Y represents N, Z represents OH, R^2 represents H and R^1 represents a bond with R^5 by treatment of a corresponding compound of formula I, where Y represents N^+R^7, Z represents O^-, R^7 represents $CH_2C_6H_4Oalkyl$ and B, D, E, G, X, Ar^1, R^1, R^2, and R^5 are as hereinbefore defined, with an acid, for example trifluoroacetic acid, for example at reflux;

(v) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents H by reaction of a compound of formula XI:



(XI)

where X represents CH_2, R^1 represents H, R^2 represents a group corresponding to R^7 as hereinbefore defined in the compound of formula I, B, D, E and G are as hereinbefore defined and R is alkyl, with a compound of formula XII:

Ar^1NHNH_2 (XII)

wherein Ar^1 is as hereinbefore defined, for example in xylene at reflux;

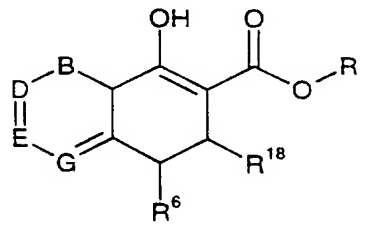
(w) preparation of compounds of formula I where X represents C=O, R^2 does not represent H, Y represents N, Z represents OH and R^1 represents a bond with R^5 by reaction of a compound of formula XI as hereinbefore defined, where X represents C=O, R^1 represents H, R^2 is as hereinbefore defined and B, D, E, G and R are as hereinbefore defined, with a compound of formula XII as hereinbefore defined, wherein Ar^1 is as hereinbefore defined, for example in xylene at reflux;

(x) preparation of compounds of formula I where X represents CH_2, Y represents N, Z represents OR^8, R^8 and R^5 form a bond and R^1 represents alkyl by reaction of a compound of formula XI as hereinbefore defined, where X represents CH_2, R^1 represents alkyl and B, D, E, G, R^2 and R are as hereinbefore defined, with a compound of formula XII as hereinbefore defined, wherein Ar^1 is as hereinbefore defined, for example in xylene at reflux; or

(y) preparation of compounds of formula I where X represents C=O, Y represents N, Z represents OR^8, R^8 and R^5 form a bond and R^1 represents alkyl by reaction of a compound of formula XI as hereinbefore defined, where X represents C=O, R^1 represents alkyl, R^2 represents H or alkyl, and B, D, E, G and R are as hereinbefore defined, with a compound of formula XII as hereinbefore defined, wherein Ar^1 is as hereinbefore defined, for example in xylene at reflux;

(z) preparation of compounds of formula I where X represents CR^3R^6, Y represents CR^{18}, Z represents OH, R^1 and R^5 form a bond and R^2 and R^3 form a bond by oxidation of a corresponding compound of formula I where X represents CR^3R^6, Y represents CR^{18}, Z represents OH, R^2 and R^3 represent H, R^1 and R^5 form a bond and B, D, E, G, Ar^1, R^6 and R^{18} are as hereinbefore defined; or

(aa) preparation of compounds of formula I where X represents CR^3R^6, Y represents CR^{18}, Z represents OH, R^2 and R^3 represent H and R^1 and R^5 form a bond by reaction a compound of formula XII as hereinbefore defined with a compound of formula XX:



(XX)

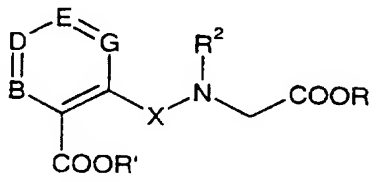
wherein B, D, E, G, R^6, R^{18} and R are as hereinbefore defined.

Compounds of formula I, wherein X represents CHR^3, R^2 and R^3 together represent a bond, R^1 and R^5 form a bond and either:

- Y represents N^+R^7 and Z represents O^-, or
- Y represents N, and Z represents OH,

may be prepared analogously to the methods described in *J. Med. Chem.* **35**, 368 (1992). Compounds of formula VIII are known from European Patent Application No. EP-A-187551, or may be prepared analogously to the methods described therein.

Compounds of formula XI may be prepared by reaction of a compound of formula XIII:

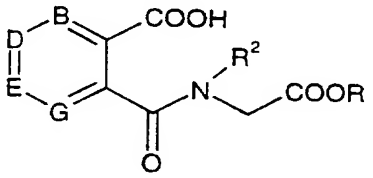


(XIII)

wherein B, D, E, G, R, R^2 and X are as hereinbefore defined and R' is alkyl, with a base, for example sodium hydride, for example in DMSO at 60 °C in the presence of an alcohol.

Compounds of formula XI wherein X represents C=O and R^2 represents H are known from Japanese Examined Patent Publication No. JP-B-82 54,152 or may prepared analogously to the methods described therein.

Compounds of formula XIII, where X represents C=O, may be prepared by reaction of a compound of formula XVI:



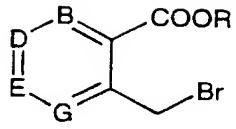
(XVI)

wherein B, D, E, G, R and R^2 are as hereinbefore defined, by alkylation, for example with a compound of formula XVII:

$$(R'O)_2SO_2 \qquad \text{(XVII)}$$

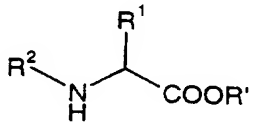
wherein R' is as hereinbefore defined, in the presence of a base, for example potassium carbonate, for example in acetone at 50 °C.

Compounds of formula XIII, where X represents CH_2, may be prepared by reaction of a compound of formula XIV:



(XIV)

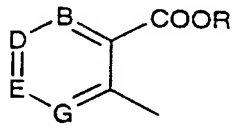
wherein B, D, E, G and R are as hereinbefore defined, with a compound of formula XV:



(XV)

wherein R^1, R^2 and R' are as hereinbefore defined, in the presence of a base for example triethylamine, in an appropriate solvent, for example ether at reflux.

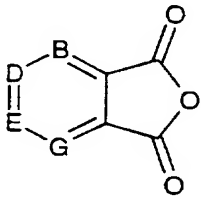
Compounds of formula XIV may be prepared by reaction of a compound of formula XVIII:



(XVIII)

wherein B, D, E, G and R are as hereinbefore defined with a brominating agent, for example NBS, for example in dichloroethane at reflux with photolytic irradiation.

Compounds of formula XVI may be prepared by reaction of a compound of formula XIX:



(XIX)

wherein B, D, E and G are as hereinbefore defined, with a compound of formula XV as hereinbefore defined, wherein R^1, R^2 and R' are as hereinbefore defined, in an appropriate solvent, for example acetone at 50 °C.

Compounds of formula II, III, IV, V, VI, VII, IX, X, XII, XV , XVI, XVII, XVIII and XX are either commercially available, are well known in the literature, or are available using known techniques.

It will be appreciated by those skilled in the art that in the process steps described above the functional groups of intermediate compounds may need to be protected by protecting groups. The protection of functional groups may take place before any the process steps hereinbefore described. For example the nitrogen atom of compounds of formula XI, XIII and XVI may

be protected before further reaction using a suitable protecting group, for example a benzyl group or preferably a 4-methoxyphenylmethyl group. Protecting groups may be removed following a reaction step or at the end of the reaction process using techniques which are well known to those skilled in the art (for example acid hydrolysis).

The compounds of the invention are useful possess pharmacological activity and are therefore indicated as pharmaceuticals useful in therapy.

According to the invention there is further provided a compound of formula I as hereinbefore defined, but without proviso (c), for use as a pharmaceutical.

In particular the compounds of the invention possess antiallergic and anti-inflammatory activity, for example as shown in the tests described below. The compounds of the invention are thus indicated for use in the treatment of allergic and inflammatory diseases of the airways such as asthma (for example bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma), particularly chronic or inveterate asthma (for example late asthma and airway hyper-responsiveness), bronchitis and the like. Further, the compounds of the invention are indicated in the treatment of diseases including inflammations/allergies such as rhinitis, including all conditions characterised by inflammation of the nasal mucus membrane, such as acute rhinitis, allergic rhinitis, atrophic rhinitis, chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta and rhinitis sicca, rhinitis medicamentosa, membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis, scrofoulous rhinitis, seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis.

The compounds of the invention are also indicated for use in the treatment of chronic allergic disorders, atopic dermatitis, cutaneous eosinophilias, eosinophilic fascitis, hyper IgE syndrome, vernal conjunctivitis, systemic lupus erythematosis, thyroiditis, lepromatous leprosy, sezary syndrome, chronic graft versus host disease, myasthenia gravis, idiopathic thrombocytopenia pupura and the like.

The compounds of the invention may also have activity in both the prophylactic and therapeutic treatment of acquired immunodeficiency syndrome (AIDS), the prevention of chronic rejection of allografts mediated by humoral immunity, and in the treatment of autoimmune diseases such as multiple sclerosis and rheumatoid arthritis.

Of particular interest amongst the above indications are the use of the compounds of the invention in asthma, especially the prophylaxis of asthma, and in rhinitis, most particularly allergic rhinitis and seasonal rhinitis including rhinitis nervosa (hay fever).

According to a further aspect of the present invention, there is provided a method of treatment or prophylaxis of an allergic or an inflammatory disorder, which method comprises administration of a therapeutically effective amount of a compound of formula I as defined above, but without provisos (b) or (c), or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to such a disease.

Administration of the compounds of the invention may be topical (for example by inhalation to the lung). The compounds of the invention may be inhaled as a dry powder which may be pressurised or non-pressurised.

In non-pressurised powder compositions, the active ingredient in finely divided form may be used in admixture with a larger sized pharmaceutically acceptable inert carrier The composition may alternatively be pressurised and contain a compressed gas, for example nitrogen, or a liquefied gas propellant. In such pressurised compositions, the active ingredient is preferably finely divided. The pressurised composition may also contain a surface active agent. The pressurised compositions may be made by conventional methods.

The compounds of the invention may be administered systemically (for example by oral administration to the gastrointestinal tract). The active ingredient may be formulated together with known adjuvants, diluents or carriers using conventional techniques to produce tablets or capsules for oral administration to the gastrointestinal tract. Examples of suitable adjuvants, diluents or carriers for oral administration in the form of tablets, capsules and dragees include microcrystalline cellulose, calcium phosphate, diatomaceous earth, a sugar such as lactose, dextrose or mantel, talc, stearic acid, starch, sodium bicarbonate and/or gelatine.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula I as hereinbefore defined, but without proviso (c), or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant diluent or carrier.

Suitable doses for administration topical or orally are in the range 0.01 to 30 mg kg^{-1} day^{-1}, for example 0.3 mg kg^{-1} day^{-1}.

It will be understood by those skilled in the art that certain functional groups in the compounds of the invention may be protected using appropriate protecting groups to form "protected derivatives" of the compounds of the invention. It will also be appreciated that, although such protected derivatives may not possess pharmacological activity as such, they may be administered and thereafter metabolised in the body to form the compound of the invention which is pharmacologically active. Such derivatives may therefore be described as "prodrugs". All protected derivatives and prodrugs of compounds of formula I are included within the scope of the invention.

The invention is illustrated by the following examples.

General Notes:

Column chromatography was run on silica (35–70μM) under gas pressure, typically 0.5 bar. The following hydrazines were used as intermediates in the subsequent examples:

5-Hydrazino-2-methylpyridine

A solution of sodium nitrite (0.3 g) in water (2 ml) was added to a cold solution of 5-amino-2-methylpyridine (*J. Chem. Soc. (C).*, 1971, 3257) (3.61 g) in water (6 ml) and concentrated hydrochloric acid (1 ml) whilst maintaining the temperature below 5 °C. The mixture was stirred at 0 °C for 15 minutes then further cooled to -10 °C. A solution of tin(II)chloride (2.53 g) in concentrated hydrochloric acid (5 ml) was then added dropwise. After stirring at -10 °C for 10 minutes the solution was allowed to warm to room temperature and anhydrous potassium carbonate was added until a thick slurry was formed. The slurry was stirred with ethyl acetate and the organic phase was decanted and evaporated to an oil. The slurry was then diluted with water and extracted with dichloromethane (thrice). The organic phase was dried over sodium sulphate, filtered and evaporated then combined with the oil above. Purification by column chromatography eluting with dichloromethane : methanol (20:1) gave the title compound as a beige solid (0.09 g). m.p. 68–70 °C

^{1}H NMR ($CDCl_3$) δ 2.47 (3H, s), 3.60 (2H, br s), 5.13 (1H, br s), 7.03 (1H, d), 7.12 (1H, dd), 8.12 (1H, d).

4-(Pentafluoroethyl)phenyl hydrazine
Prepared following the method used for 5-Hydrazino-2-methylpyridine using 4-(pentafluoroethyl)aniline (*J. Chem. Soc., Perkin Trans.* **1**, 1990, 2293). MS (EI) 226 (M^+) ^{1}H NMR ($CDCl_3$) δ 4.15 (2H, br), 6.87 (2H, d), 7.30 (2H, d), 7.45 (1H, br)

2-Hydrazino-5-methylpyridine (*J. Org. Chem.*, 1966, **31**, 251)

2-Chloro-5-hydrazinopyridine (*Atti R. Accad. dei Lincei*, Roma, 1925, **2**, 125); *Chem. Zent.* 1926, I, 672

2-Hydrazinopyrimidine *J. Chem. Soc.* 1955, 3478

Example 1

3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt

(a) Methyl 2-[*N*-(methoxycarbonylmethyl)-*N*-(4-methoxyphenyl)methyl)amino]methylbenzoate.

Methyl 2-bromomethylbenzoate (23.47 g; prepared analogously to the method described for the ethyl ester in *J. Med. Chem.*, 1992, **35**, 368) and triethylamine (15.7 ml) were dissolved in dry diethyl ether (200 ml) under a nitrogen atmosphere. Methyl *N*-[(4-methoxyphenyl)methyl] glycinate (23.6 g; *J. Am. Chem. Soc.*, 1993, **115**, 536) was added dropwise. The mixture was heated under reflux for 16 hours and allowed to cool to room temperature. Water was added and the organic phase was separated. The aqueous phase was then extracted with ethyl acetate (thrice). The combined organic phase was washed with brine and dried over sodium sulfate. Filtration and evaporation of the solution followed by further purification of the residues by column chromatography, eluting with ethyl acetate : isohexane (1:9), gave the subtitle compound as an oil (27.85 g) ; MS(APCI) 358 ($(M+H)^+$)
^{1}H NMR ($CDCl_3$); δ 3.23 (2H, s), 3.66 (3H, s), 3.71 (2H, s), 3.78 (3H, s), 3.88 (3H, s), 4.16 (2H, s), 6.8 (2H, d), 7.2 (2H, d), 7.3 (1H, td), 7.45 (1H, td), 7.6 (1H, dd), 7.75 (1H, dd).

(b) Methyl 1,2,3,4-tetrahydro-2-(4-methoxyphenyl)methyl-4-oxo-3-isoquinolinecarboxylate

Methyl-2-[*N*-(methoxycarbonylmethyl)-*N*-(4-methoxyphenyl)methyl)amino]methylbenzoate (27.85 g; from step (a) above) was dissolved in dry toluene (150 ml) and added

dropwise to a refluxing suspension of oil-free sodium hydride (from 4.37g of 60% sodium hydride) in dry toluene (300 ml) and 2-methylpropan-2-ol (2.0 ml). The heating was continued for 12 hours. The mixture was allowed to cool to room temperature and was then poured onto saturated ammonium chloride solution and extracted with ethyl acetate (thrice). The combined organic phase was then washed with brine and dried over sodium sulfate. Filtration and evaporation followed by purification by column chromatography, eluting with diethyl ether : isohexane (1:4), gave the subtitle compound as an oil (20.41 g). ^{1}H NMR ($CDCl_3$) (major component—enol tautomer) δ 3.60 (2H, s), 3.81 (3H, s), 3.91 (5H, s), 6.86 (2H, d), 7.09 (1H, d), 7.25 (2H, d), 7.35–7.43 (2H, m), 7.77 (1H, d) and 11.58 (1H, s).

(c)

3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt

Methyl 1,2,3,4-tetrahydro-2-(4-methoxyphenyl)methyl-4-oxo-3-isoquinolinecarboxylate (1.0 g; from step (b) above), 4-(trifluoromethyl)phenylhydrazine (1.08 g) and a catalytic amount of 4-toluenesulfonic acid were fused together at 150 °C for 10 minutes. Xylene (20 ml) was then added and heating was continued for a further 1 hour. After cooling to room temperature the solvent was evaporated. The solid residue was triturated with diethyl ether to give the title compound as a red solid (0.5 g). m.p. 220–221 °C

MS(APCI) 450 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) δ 3.72 (3H, s), 6.08 (2H, s), 6.95 (2H, m), 7.7 (2H, m), 7.8 (3H, m), 7.95 (1H, td), 8.15 (1H, d), 8.35 (1H, d), 8.6 (2H, d), 8.96 (1H, s).

Example 2

2-(4-Trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt (0.26 g; from step (c) above) was heated at reflux in trifluoroacetic acid (2 ml) under a nitrogen atmosphere for 16 hours. After cooling to room temperature the solvent was evaporated. Toluene was added to the residue and then evaporated (twice). Methanol was added and evaporated and the red residue was triturated with ethyl acetate. Recrystallisation from ethanol gave the title compound as a red solid (14 mg). m.p. >250 °C

MS (APCI) 330 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) δ 7.9 (3H, m), 8.0 (1H, t), 8.3 (4H, m), 9.03 (1H, bs).

Example 3

2-(4-Chlorophenyl)-2,5-dihydro-5-methyl-3*H*-pyrazolo[4,3-*c*]cinnolin-3-one.

2-(4-Chlorophenyl)-2,5-dihydro-pyrazolo[4,3-*c*]cinnolin-3-one (0.33 g; European Patent Application EP-A-0187551) was added portionwise to a stirred suspension of oil free sodium hydride (from 49 mg of 60% dispersion) in dry dimethylformamide (5 ml) under a nitrogen atmosphere. Iodomethane (0.076 ml) was added dropwise after 0.5 h and the resulting solution was stirred at room temperature for 2 h. The solution was poured into brine and extracted with dichloromethane/methanol (thrice). The organic phase was washed with 2M hydrochloric acid and brine, and then dried over sodium sulfate, filtered and concentrated to give a red solid. Purification by column chromatography (3:2 ethyl acetate : hexane), followed by recrystallisation from dimethylformamide, gave the title compound as red crystals (55 mg).

m.p. >250 °C

MS(EI) 310, 312 (M^+)

^{1}H NMR ($CDCl_3$) δ 4.33 (3H, s), 7.4 (2H, dd), 7.65 (2H, t), 7.75 (1H, td), 8.20 (2H, dd), 8.35 (1H, d).

Example 4

2-(4-Chlorophenyl)-2,3a,4,5-tetrahydro-3a,4-dimethylpyrazolo[4,3-*c*]isoquinolin-3-one

(a) Methyl 2-[((1-methoxycarbonyl)ethyl)methylamino]methyl benzoate

Methyl 2-bromomethylbenzoate (3.51 g) and diisopropylethylamine (5.86 ml) were dissolved in dry diethyl ether (30 ml) under a nitrogen atmosphere and the solution was cooled to 0 °C. *N*-methylalanine methyl ester trifluoroacetic acid salt (3.89 g) dissolved in

dry diethyl ether (10 ml) and dry dichloromethane (5 ml) was added dropwise and the mixture was allowed to warm to room temperature overnight. Water was then added and the organic phase separated, washed with brine and dried over sodium sulfate. Filtration and evaporation followed by column chromatography (1:9 ethyl acetate : hexane) gave the subtitle compound (2.87 g).

MS (EI) 265 (M^+)

(b) Methyl 1,2,3,4-tetrahydro-2,3-dimethyl-4-oxo-3-isoquinoline carboxylate

Methyl 2-[((1-methoxycarbonyl)ethyl)methylamino]methylbenzoate (2 g) in dry toluene (10 ml) was added dropwise to a refluxing suspension of oil free sodium hydride (from 0.42 g of 60% dispersion) in dry toluene (30 ml) and 2-methyl-2-propanol (5 drops) under a nitrogen atmosphere. After being heated at reflux for 45 minutes the solution was cooled in ice and poured into saturated ammonium chloride solution which was extracted with ethyl acetate (thrice). The organic phase was washed with brine and dried over sodium sulfate. Filtration and evaporation followed by column chromatography (1:4 ethyl acetate : hexane) gave the subtitle compound as a yellow oil (0.95 g).

MS (EI) 234 ($(M+H)^+$)

(c) 2-(4-Chlorophenyl)-2,3a,4,5-tetrahydro-3a,4-dimethylpyrazolo[4,3-*c*]isoquinolin--3-one

Methyl 1,2,3,4-tetrahydro-2,3-dimethyl-4-oxo-3-isoquinolinecarboxylate (0.84 g), 4-chlorophenylhydrazine (1.54 g) and 4-toluenesulfonic acid (20 mg) were fused together at 150 °C for 10 minutes under a nitrogen atmosphere. Xylene (10 ml) was then added and the mixture was heated at 150 °C a further 6 hours. After cooling to room temperature the solvent was removed and the residue was dissolved in dichloromethane/methanol. The solution was washed with 2M hydrochloric acid and brine, then dried over sodium sulfate. Filtration and evaporation followed by column chromatography (1:99 methanol : dichloromethane) gave the title compound as a colourless solid (50 mg).

m.p. 128–129 °C.

MS (EI) 325, 327 (M^+)

Example 5

2-(4-Chlorophenyl)-3a,4-dihydro-3a,4-dimethyl-2*H*-pyrazolo[4,3-*c*]isoquinoline--3,5-dione

(a) Methyl 1,2,3,4-tetrahydro-2,3-dimethyl-1,4-dioxo-3-isoquinolinecarboxylate

Methyl 1,2-dihydro-4-hydroxy-2-methyl-1-oxo-3-isoquinoline carboxylate (JP-B-82 54,152; 1.5 g) in dry dimethylformamide (5 ml) was added dropwise to a stirred suspension of oil free sodium hydride (from 0.28g 60% dispersion) in dry dimethylformamide (10 ml) at room temperature under a nitrogen atmosphere. After 30 minutes, iodomethane (0.4 ml) was added dropwise. The solution was stirred at room temperature for 3 hours, then poured into 2M hydrochloric acid and extracted with ethyl acetate (thrice). The organic phase was washed with brine and dried over sodium sulfate. Filtration and evaporation followed by column chromatography (1:1 diethyl ether : hexane) gave the subtitle compound as a yellow oil (0.53 g).
MS (ESI) 248 ($(M+H)^+$)

(b) 2-(4-Chlorophenyl)-3a,4-dihydro-3a,4-dimethyl-2*H*-pyrazolo[4,3-*c*]isoquinoline--3,5-dione

Methyl 1,2,3,4-tetrahydro-2,3-dimethyl-1,4-dioxo-3-isoquinolinecarboxylate (0.53 g), 4-chlorophenylhydrazine (0.92 g) and 4-toluenesulfonic acid (10 mg) were fused together at 150 °C under a nitrogen atmosphere for 10 minutes. Xylene (5 ml) was then added and the mixture was heated at 150 °C for 10 hours. After cooling to room temperature the solvent was removed and the residue dissolved in dichloromethane/methanol, was washed with 2M hydrochloric acid, sodium bicarbonate solution and brine. The solution was dried over sodium sulfate, filtered and evaporated. Purification by column chromatography (1:9 ethyl acetate : hexane) followed by recrystallisation from propan-2-ol gave the title compound as a beige solid (0.13 g). m.p. 192–193 °C
MS (EI) 339, 341 (M^+)

Example 6

2-(4-Chlorophenyl)-2,4-dihydro-3-hydroxy-4-methylpyrazolo[4,3-*c*]isoquinolin-5-one

Methyl 1,2-dihydro-4-hydroxy-2-methyl-1-oxo-3-isoquinolinecarboxylate (JP 82 54,152; 0.5 g), 4-chlorophenylhydrazine (0.91 g) and 4-toluenesulfonic acid (10 mg) were fused together at 150 °C for 10 minutes under a nitrogen atmosphere. Xylene (5 ml) was then added and the mixture heated at 150 °C for 5 hours. After cooling to room temperature a yellow precipitate was collected by filtration and washed with diethyl ether. Purification by

column chromatography (1:49 methanol : dichloromethane) followed by recrystallisation from ethanol gave the title compound as a beige solid (0.1 g). m.p. >250°C
MS (EI) 325, 327 (M^+)

Example 7

3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-(3-quinolyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt.

The title compound was prepared according to the method described in Example 1(c) using 3-hydrazinoquinoline. m.p. 232–233 °C.
MS (APCI) 433 ($(M+H)^+$)
NMR (d_6-DMSO) δ 3.7 (3H, s), 6.1 (2H, s), 6.7 (2H, d), 7.65 (1H, t), 7.70 (3H, m), 7.80 (1H, t), 8.05 (3H, m), 8.20 (1H, d), 8.40 (1H, d), 9.00 (1H, s), 9.20 (1H, d), 9.90 (1H, d).

Example 8

2-(3-Quinolyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

The title compound (0.21 g) was prepared according to the method described in Example 2 using 3-hydroxy-4-[(4-methoxyphenyl)methyl]-2-(3-quinolyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt (0.66 g). m.p. 247–248 °C
MS (APCI) 313 ($(M+H)^+$)
^{1}H NMR (d_6-DMSO) δ 7.70 (1H, td), 7.80 (1H, td), 7.90 (1H, bt), 8.00 (1H, t), 8.15 (2H, m), 8.35 (2H, m), 8.90 (1H, d), 9.05 (1H), 9.70 (1H, d), 12.20 (1H, bs)

Example 9

2-(3,4-Dichlorophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt

The title compound was prepared according to the method described in Example 1(c) using 3,4-dichlorophenylhydrazine. m.p. 239–240 °C
MS (APCI) 448, 450, 452 ($(M+H)^+$)
^{1}H NMR (d_6-DMSO): δ 3.72 (3H, s), 6.06 (2H, s), 6.96 (2H, d), 7.70 (3H, m), 7.79 (1H, t), 7.97 (1H, t), 8.16 (1H, d), 8.37 (2H, m), 8.72 (1H, d), 8.97 (1H, s).

Example 10

2-(3,4-Dichlorophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

The title compound (0.028 g) was prepared according to the method described in Example 2 using 2-(3,4-dichlorophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt (0.26 g). m.p. >230 °C.

MS (APCI) 330, 332, 334 ($(M+H)^+$)
^{1}H NMR (d_6-DMSO) δ 7.82 (1H, d), 7.86 (1H, t), 7.97 (1H, t), 8.13 (1H, dd), 8.24 (1H, d), 8.32 (1H, d), 8.42 (1H, d), 8.94 (1H, s).

Example 11

2-([1,1'-Biphenyl]-4-yl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

(a) 2-([1,1'-Biphenyl]-4-yl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt

The sub-title compound was prepared according to the method described in Example 1(c) using [1,1'-biphenyl]-4-ylhydrazine (see *J. Chem. Soc., Perkin Trans.* **I**, (1975) 1280).

(b) 2-([1,1'-Biphenyl]-4-yl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

The title compound (0.082 g) was prepared according to the method described in Example 2 using 2-([1,1'-biphenyl]-4-yl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt (0.29 g; from step (a) above).
m.p. >220° (dec.).
MS (APCI) 338 ($(M+H)^+$)
^{1}H NMR (d_6-DMSO) δ 7.37 (1H, m), 7.51 (2H, m), 7.75 (2H, m), 7.89 (3H, m), 7.98 (1H, m), 8.05 (2H, m), 8.31 (2H, m), 9.02 (1H, s, br)

Example 12

3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-methylphenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt

The title compound was prepared according to the method described in Example 1(c) using 4-methylphenylhydrazine.
m.p. >100 °C (dec.)
MS (APCI) 396 ($(M+H)^+$)
^{1}H NMR (d_6-DMSO) δ 2.34 (3H, s), 3.72 (3H, s), 6.10 (2H, s), 6.96 (2H, m), 7.26 (2H, m), 7.74 (3H, m), 7.94 (1H, m), 8.13 (1H, d), 8.23 (2H, d) 8.33 (1H, d), 8.89 (1H, s)

Example 13

2-(4-Methylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

The title compound (0.043 g) was prepared according to the method described in Example 2 using 3-hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-methylphenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt (0.20 g). m.p. 202–209 °C (dec.).
MS (APCI) 276 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) δ 2.37 (3H, s), 7.37 (2H, d), 7.88 (3H, m), 7.94 (1H, m), 8.29 (2H, m), 9.02 (1H, br), 11.90 (1H, br)

Example 14

2-(4-Bromophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt

The title compound was prepared according to the method described in Example 1(c) using 4-bromophenylhydrazine. m.p. >220 °C (dec.).

MS (APCI) 460, 462 ($(M+H)^+$).

^{1}H NMR (d_6-DMSO) δ 3.70 (3H, s), 6.08 (2H, s), 6.96 (2H, m), 7.66 (2H, m), 7.76 (2H, m), 7.77 (1H, t), 7.96 (1H, m), 8.15 (1H, d), 8.36 (3H, m), 8.94 (1H, s)

Example 15

2-(4-Bromophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

The title compound (0.053 g) was prepared according to the method described in Example 2 using 2-(4-bromophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt (0.164 gm.p. > 250 °C.

MS (APCI) 340, 342 ($(M+H)^+$).

^{1}H NMR (d_6-DMSO) δ 7.76 (2H, d), 7.89 (1H, m), 8.02 (3H, m), 8.31 (2H, m), 9.07 (1H, br), 11.92 (1H, br)

Example 16

2-(3-Trifluoromethylphenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt

The title compound was prepared according to the method described in Example 1(c) using 3-trifluoromethylphenylhydrazine to give an oil which was purified twice by chromatography, eluting the first time with ethyl acetate and the second time with ether : ethyl acetate mixtures, to give the title compound as an oil.

MS (APCI) 450 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 6.19 (2H, s), 6.96 (2H, d), 7.45 (1H, m), 7.54 (3H, m), 7.79 (2H, m), 7.86 (1H, t), 8.52 (1H, d), 8.68 (1H, d), 8.72 (1H, s)

Example 17

2-(3-Trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

The title compound was prepared according to the method described in Example 2 using 2-(3-trifluoromethylphenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt. m.p. 250 °C dec.

MS (APCI) 330 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) δ 7.67 (1H, d), 7.81 (1H, t), 7.88 (1H, t), 7.99 (1H, t), 8.42 (3H, m), 8.48 (1H, s), 9.01 (1H, s)

Example 18

2-[4-(1,1-Dimethylethyl)phenyl]-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

(a) 3-Hydroxy-2-[4-(1,1-dimethylethyl)phenyl]-4-[(4-methoxyphenyl)methyl]-2*H*--pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt

The sub-title compound was prepared according to the method described in Example 1(c) using 4-[(1,1-dimethylethyl)phenyl]hydrazine and was used without further purification in the proceeding step.

(b) 2-[4-(1,1-Dimethylethyl)phenyl]-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

The title compound was prepared according to the method described in Example 2 using 3-hydroxy-2-[4-(1,1-dimethylethyl) phenyl]-4-(4-methoxyphenylmethyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt. m.p. >210° (dec.).

MS (APCI) 318 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) δ 1.33 (9H, s), 7.51 (2H, d), 7.75 (1H, t), 7.84 (1H, t), 8.01 (2H, d), 8.12 (1H, d), 8.25 (1H, d), 8.74 (1H, s)

Example 19

2-(4-Trifluoromethoxyphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

(a) 2-(4-Trifluoromethoxyphenyl)-3-Hydroxy-2-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt

The sub-title compound was prepared according to the method described in Example 1(c) using 4-trifluoromethoxyphenylhydrazine and was used without further purification in the proceeding step.

(b) 2-(4-Trifluoromethoxyphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

The title compound was prepared according to the method described in Example 2 using 2-(4-trifluoromethoxyphenyl)-3-hydroxy-2-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt. m.p. > 230 °C.
MS (APCI) 346 ($(M+H)^+$)
^{1}H NMR (d_6-DMSO) δ 7.58 (2H, d), 7.91 (1H, t), 7.99 (1H, t), 8.14 (2H, d), 8.29 (2H, m), 9.03 (1H, br s).

Example 20

2-(4-Chlorophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt.

Methyl 1,2,3,4-tetrahydro-2-methyl-4-oxo-3-isoquinolinecarboxylate (0.5 g) (I. G. Hinton & F. G. Mann, *J. Chem. Soc.* 1959, 599), 4-chlorophenylhydrazine (0.98 g) and 4-toluenesulfonic acid (10 mg) were fused together at 150 °C for ten minutes under a nitrogen atmosphere. Xylene (10 ml) was then added and the mixture was heated for a further 6 h at 150 °C. The reaction mixture was cooled and the resulting red precipitate filtered off and washed with diethyl ether. Recrystallisation from methanol gave the title compound (0.27 g). m.p. 247–248 °C.
MS (EI) 309, 311 (M^+).
^{1}H NMR (d_6-DMSO) δ 4.5 (3H, s), 7.5 (2H, d), 7.75 (1H, t), 7.95 (1H, t), 8.1 (1H, d), 8.3 (1H, d), 8.4 (2H, d), 8.6 (1H, s).

Example 21

2-(4-Chlorophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]cinnolinium hydroxide, inner salt.

2-(4-Chlorophenyl)-2,5-dihydro-pyrazolo[4,3-*c*]cinnolin-3-one (0.33 g) (European Patent Application EP-A-0187551) was added portionwise to a stirred suspension of oil free sodium hydride (from 49 mg 60% dispersion) in dry dimethylformamide (5 ml) under a nitrogen atmosphere. Iodomethane (0.076 ml) was added dropwise after 0.5 h and the resulting solution was stirred at room temperature for 2 h. The solution was poured into brine and extracted with dichloromethane/methanol mixtures (thrice). The organic phase was washed with 2N hydrochloric acid and brine then dried over sodium sulfate, filtered and concentrated to give a red solid. Purification by column chromatography (2:3 ethyl acetate : hexane), followed by recrystallisation from dimethylformamide gave the title compound as purple crystals (65 mg). m.p. 249–250 °C.
MS (EI) 310, 312 (M^+).

^{1}H NMR ($CDCl_3$) 4.81 (3H, s), 7.40 (2H, d), 7.75 (2H, m), 8.00 (1H, dd), 8.25 (2H, d), 8.35 (1H, dd).

Example 22

2-(4-Chlorophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt.

The title compound was prepared according to the method described in Example 20, from methyl 1,2,3,4-tetrahydro-2-(4-methoxyphenyl)methyl-4-oxo-3-isoquinolinecarboxylate (which latter compound was prepared analogously to the methods described in I. G. Hinton & F. G. Mann, *J. Chem. Soc.* 1959, 599). m.p. 227–228 °C.
MS (EI) 416, 418 ($(M+H)^+$).
^{1}H NMR (d_6-DMSO) 3.70 (3H, s), 6.08 (2H, s), 6.95 (2H, d), 7.50 (2H, d), 7.70 (2H, d), 7.75 (1H, t), 7.95 (1H, t), 8.15 (1H, d), 8.35 (1H, d), 8.40 (2H, d), 8.93 (1H, s).

The following compounds, Examples 23–56, were prepared by methods analogous to examples 20 & 22:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
23	3-Hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	201–203	344 $(M+H)^+$	4.51 (3H, s), 7.80 (3H, m), 7.97 (1H, t), 8.10 (1H, d), 8.35 (1H, d), 8.60(2H, d), 8.66(1H, s).
24	3-Hydroxy-4-methyl-2--(3-quinolyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	327 $(M+H)^+$	4.55 (3H, s), 7.60 (1H, td), 7.70 (1H, td), 7.82 (1H, td), 8.00 (3H, m), 8.10 (1H, d), 8.40 (1H, d), 8.69 (1H, s), 9.13 (1H, d), 9.93 (1H, d).
25	2-(6-Chloro-3-pyridyl)-3--hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	311/313 $(M+H)^+$	4.50(3H, s), 7.61(1H, d), 7.80(1H, t), 7.97(1H, t), 8.12(1H, d), 8.35(1H, d), 8.68(1H, s), 8.74(1H, dd), 9.37(1H, s)
26	2-(3,4-Dichlorophenyl)-3--hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	223–229	344/346/348 $(M+H)^+$	4.49 (3H, s), 7.70 (1H, d), 7.78 (1H, t), 7.96 (1H, t), 8.11 (1H, d), 8.35 (2H, m), 8.67 (2H, m)

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
27	3-Hydroxy-4-methyl-2-(4--methylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt	247–248	290 $(M+H)^+$	2.33 (3H, s), 4.52 (3H, s), 7.24 (2H, m), 7.74 (1H, m), 7.93 (1H, m), 8.09 (1H, m), 8.20 (2H, m), 8.33 (1H, d), 8.59 (1H, s)
28	2-(4-Bromophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt	244	354/356 $(M+H)^+$	4.50 (3H, s), 7.63 (2H, d), 7.76 (1H, t), 7.96 (1H, t), 8.10 (1H, d), 8.34 (3H, m), 8.63 (1H, s)
29	3-Hydroxy-4-methyl-2-(3-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	222–6	344 $(M+H)^+$	4.51 (3H, s), 7.53 (1H, d), 7.69 (1H, t), 7.78 (1H, t), 7.96 (1H, t), 8.12 (1H, d), 8.35 (1H, d), 8.63 (1H, d), 8.66 (1H, s), 8.81 (1H, s)
30	2-[4-(1,1-Dimethylethyl)-phenyl]-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>220° (dec.)	332 $(M+H)^+$	1.35 (9H, s), 4.65 (3H, dt), 7.46 (2H, m), 7.62 (1H, dt), 7.71 (1H, s), 7.83 (2H, m), 8.15 (2H, m), 8.50 (1H, d) ($CDCl_3$ not DMSO d_6)
31	2-(6-Chloro-3-pyridyl)--3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt	223–224	417/419 $(M+H)^+$	3.72 (3H, s), 6.07 (2H, s), 6.97 (2H, d), 7.62 (1H, d), 7.70 (2H, d), 7.81 (1H, t), 8.00 (1H, t), 8.16 (1H, d), 8.36 (1H, d), 8.79 (1H, dd), 8.98 (1H, dd), 9.38 (1H, d)
32	3-Hydroxy-4-methyl-2-(6--methyl-3-pyridyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	291 (M+H)	2.50 (3H, s), 4.51 (3H, s), 7.33 (1H, d), 7.77 (1H, t), 7.98 (1H, t), 8.10 (1H, d), 8.34 (1H, d), 8.50 (1H, dd), 8.64 (1H, s), 9.38 (1H, d)
33	2-(4- trifluoromethylphenyl)--3-hydroxy-4-(2-hydroxyethyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	374 $(M+H)^+$	3.99 (2H, m), 4.92 (2H, m), 5.19 (1H, t), 7.79 (3H, m), 7.99 (1H, m), 8.20 (1H, d), 8.38 (1H, d), 8.60 (2H, d), 8.65 (1H, s)

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
34	3-Hydroxy-4-methyl-2-(5--methyl-2-pyridyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	237–240	291 $(M+H)^+$	2.34 (3H, s), 4.50 (3H, s), 7.75 (2H, m), 7.98 (1H, t), 8.11 (1H, d), 8.18 (1H, d), 8.36 (1H, d), 8.40 (1H, d), 8.59 (1H, s)
35	3-Hydroxy-4-methyl-2-[4-(1--methylethyl)phenyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	171–172	318 $(M+H)^+$	1.25 (6H, d), 2.92 (1H, m), 4.53 (3H, s), 7.34 (2H, d), 7.78 (1H, t), 7.97 (1H, t), 8.14 (3H, m), 8.35 (1H, d), 8.69 (1H, s)
36	3-Hydroxy-4-methyl-2-(4--nitrophenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt	>230	321 $(M+H)^+$	3.93 (3H, s), 7.79 (1H, t), 7.99 (1H, t), 8.12 (1H, d), 8.33 (3H, m), 8.62 (2H, d), 8.71 (1H, s)
37	2-(4-Cyanophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt	225–227	301 $(M+H)^+$	4.49 (3H, s), 7.79 (1H, t), 7.89 (2H, t), 7.95 (1H, t), 8.00 (1H, d), 8.34 (1H, d), 8.56 (2H, d), 8.67 (1H, s).
38	2-(4-Carboxyphenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt	>230	320 $(M+H)^+$	4.51 (3H, s), 7.78 (1H, t), 7.99 (1H, t), 8.01 (2H, d), 8.12 (1H, d), 8.09 (1H, d), 8.47 (2H, d), 8.64 (1H, s), 12.74 (1H, s)
39	2-(4-Chloro-3-trifluoromethylphenyl)-3-hydroxy--4-methyl-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt	>230	378/380 $(M+H)^+$	4.50 (3H, s), 7.81 (2H, m), 8.00 (1H, t), 8.13 (1H, t), 8.38 (1H, d), 8.59 (1H, dd), 8.68 (1H, s), 8.98 (1H, d)
40	2-(4-Trifluoromethoxyphenyl)-3-hydroxy-4-methyl--2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	195–196	360 $(M+H)^+$	4.51 (3H, s), 7.46 (2H, d), 7.79 (1H, t), 7.96 (1H, t), 8.12 (1H, d), 8.35 (1H, d), 8.45 (2H, d), 8.64 (1H, s)

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
41	3-Hydroxy-4-methyl-2-(4--methylthiophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	197–198	322 $(M+H)^+$	2.50 (3H, s), 4.51 (3H, s), 7.33 (2H, d), 7.72 (1H, t), 7.91 (1H, t), 8.08 (1H, d), 8.27 (2H, d), 8.31 (1H, d), 8.60 (1H, s)
42	4-Cyclopropyl-3-hydroxy-2--(4-trifluoromethylphenyl)--2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	370 $(M+H)^+$	1.33 (2H, m), 1.54 (2H, m), 5.03 (1H, m), 7.78 (3H, m), 7.96 (1H, m), 8.15 (1H, d), 8.34 (1H, d), 8.61 (2H, m), 8.65 (1H, s)
43	4-Cyclopropyl-3-hydroxy-2--(6-methyl-3-pyridyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	226–240	317 $(M+H)^+$	1.32 (2H, d), 1.54 (2H, m), 2.51 (3H, s), 5.08 (1H, m), 7.33 (1H, d), 7.56 (1H, td), 7.94 (1H, td), 8.13 (1H, d), 8.32 (1H, d), 8.54 (1H, dd), 8.62 (1H, s), 9.40 (1H, d)
44	4-[(1,1-Dimethyl-2-hydroxy)-ethyl]-3-hydroxy-2-[(4-trifluoromethyl)phenyl]-2*H*-pyrazolo [4,3-*c*]isoquinolinium hydroxide, inner salt	>220	402 $(M+H)^+$	1.94 (6H, s), 4.28 (2H, d), 5.15 (1H, t), 7.79 (3H, m), 8.00 (1H, m), 8.37 (2H, t), 8.62 (2H, d), 8.77 (1H, s)
45	3-Hydroxy-4-(2-methoxy-ethyl)-2-[(4-trifluoromethyl)-phenyl]-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt	195–197	388 $(M+H)^+$	3.28 (3H, s), 3.96 (2H, t), 5.06 (2H, t), 7.79 (3H, m), 7.99 (1H, m), 8.18 (1H, d), 8.37 (1H, d), 8.58 (2H, d), 8.71 (1H, s)
46	2-(4-Chlorophenyl)-3-hydroxy-4-[2-(methylthio)ethyl]--*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	187–188	370/372 $(M+H)^+$	2.19 (3H, s), 3.20 (2H, t), 5.03 (2H, t), 7.50 (2H, m), 7.79 (1H, m), 7.99 (1H, m), 8.15 (1H, d), 8.38 (3H, m), 8.77 (1H, s)

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
47	3-Hydroxy-4-[2-(methylthio)-ethyl]-2-(4-trifluoromethyl-phenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt	193–195	404 $(M+H)^+$	2.20 (3H, s), 3.21 (2H, t), 5.04 (2H, t), 7.81 (3H, m), 8.01 (1H, m), 8.17 (1H, d), 8.39 (1H, d), 8.59 (2H, d), 8.80 (1H, s)
48	4-Cyclopropyl-2-(4-trifluoro-methoxyphenyl)-3-hydroxy--2*H*-pyrazolo[4,3-*c*]iso-quinolinium hydroxide, inner salt	188–189	386 $(M+H)^+$	1.34 (2H, m), 1.54 (2H, m), 5.08 (1H, m), 7.46 (2H, d), 7.78 (1H, t), 7.95 (1H, t), 8.15 (1H, d), 8.31 (1H, d), 8.46 (2H, d), 8.62 (1H, s)
49	2-(4-Chloro-3-trifluoro-methylphenyl)-4-cyclopropyl--3-hydroxy-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydr-oxide, inner salt	>220	404/406 $(M+H)^+$	1.33 (2H, m), 1.53 (2H, m), 4.98 (1H, m), 7.78 (2H, m), 7.97 (1H, t), 8.17 (1H, d), 8.36 (1H, d), 8.62 (1H, dd), 8.67 (1H, s), 9.03 (1H, dd)
50	4-Cyclopropyl-3-hydroxy-2--(4-methylthiophenyl)-2*H*-pyr azolo[4,3-*c*]isoquinolinium hydroxide, inner salt	166–167	348 $(M+H)^+$	1.30 (2H, m), 1.51 (2H, m), 2.51 (3H, s), 5.24 (1H, m), 7.37 (2H, d), 7.74 (1H, t), 7.93 (1H, t), 8.14 (1H, d), 8.33 (3H, m), 8.58 (1H, s)
51	3-Hydroxy-4-phenyl-2-(4-tri-fluoromethylphenyl)-2*H*-pyr-azolo[4,3-*c*]isoquinolinium hydroxide, inner salt	255	406 $(M+H)^+$	7.69(3H, m), 7.76(2H, m), 7.82(3H, m), 8.05(1H, m), 8.25(1H, d), 8.45(1H, d), 8.53(2H, m), 8.85(1H, s)
52	4-Ethyl-3-Hydroxy-2-(4-tri-fluoromethylphenyl)-2*H*-pyr-azolo[4,3-*c*]isoquinolinium hydroxide, inner salt	192–198	358 $(M+H)^+$	1.63 (3H, d), 4.88 (2H, quart), 7.75 (1H, t), 7.79 (2H, d), 7.96 (1H, t), 8.09 (1H, d), 8.33 (1H, d), 8.59 (2H, d), 8.76 (1H, s)
53	2-(4-Trifluoromethylphenyl)--4-(1-ethoxycarbonylmethyl)-3-hydroxy-2*H*-pyr-azolo[4,3-*c*]isoquinolinium hydroxide, inner salt	167–169	416 $(M+H)^+$	1.27 (3H, t), 4.27 (2H, q), 5.83 (2H, s), 7.82 (2H, d), 7.82 (1H, t), 8.04 (1H, t), 8.17 (1H, d), 8.39 (1H, d), 8.54 (2H, d), 8.71 (1H, d)

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
54	3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-phenyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	foam	382 $(M+H)^+$	3.72 (3H, s), 6.10 (2H, s), 6.95 (2H, d), 7.20 (1H, t), 7.48 (2H, t), 7.75 (3H, m), 7.95 (1H, t), 8.15 (1H, d), 8.35 (3H, m), 8.91 (1H, s)
55	3-Hydroxy-4-(1-methylethyl)--2-(4-trifluoromethylphenyl)--2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	201–203	372 $(M+H)^+$	1.70 (6H, d), 6.26 (1H, br s), 7.79 (1H, t), 7.79 (2H, d), 7.98 (1H, t), 8.22 (1H, d), 8.38 (1H, d), 8.62 (2H, d), 8.93 (1H, d)
56	3-Hydroxy-4-(1-methylethyl)--2-(3-trifluoromethylphenyl)--2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	220–222	372 $(M+H)^+$	1.71 (6H, d), 6.27 (1H, br s), 7.54 (1H, d), 7.70 (1H, t), 7.78 (1H, t), 7.96 (1H, t), 8.22 (1H, d), 8.40 (1H, d), 8.64 (1H, d), 8.85 (1H, s), 8.94 (1H, s)

Example 57

3-Hydroxy-2-(4-iodophenyl)-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt

Methyl 1,2,3,4-tetrahydro-2-methyl-4-oxo-3-isoquinolinecarboxylate (0.485 g) and 4-iodophenylhydrazine (1.053 g) were combined in ethanol (15 ml) and heated to reflux for 20 h. A solid precipitated on cooling, this was crystallised from ethanol and then propan-2-ol to give the title compound (0.054 g). m.p. >260 °C.

MS (+ve ESI) 402 ($(M+H)^+$).

^{1}H NMR (d_6-DMSO): δ 4.50 (3H, s), 7.76 (1H, t), 7.77 (2H, d), 7.94 (1H, t), 8.09 (1H, d), 8.19 (2H, d), 8.32 (1H, d), 8.62 (1H, s)

The following compounds, examples 58–60, were prepared following methods analogous to that used for example 2:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
58	2-(6-Chloro-3-pyridyl)--2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol	> 250	297/299 $(M+H)^+$	7.71 (1H, d), 7.89 (1H, t), 8.00 (1H, t), 8.31 (2H, m), 8.56 (1H, br d), 9.00 (1H, br s), 9.13 (1H, s)
59	2-[4-(1-Methylethyl)-phenyl]-2*H*-pyrazolo-[4,3-*c*]isoquinolin-3-ol	218–219	304 $(M+H)^+$	1.25 (6H, d), 2.97 (1H, m), 7.42 (2H, d), 7.93 (4H, m), 8.27 (2H, m), 9.00 (1H, s)
60	2-(4-Pentafluoroethyl-phenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolin-3-ol	219–223	380 $(M+H)^+$	7.68 (1H, t), 7.76 (3H, m), 8.02 (1H, d), 8.24 (1H, d), 8.54 (3H, m)

The following compounds, examples 61–68, were prepared following methods analogous to that used for example 6:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
61	2,4-Dihydro-3-hydroxy-4--methyl-2-(2-pyrimidinyl)-5*H*--pyrazolo[4,3-*c*]isoquinolin-5--one	>250	294 $(M+H)^+$	3.79 (3H, s), 7.48 (1H, t), 7.75 (1H, t), 7.89 (1H, t), 8.18 (1H, d), 8.35 (1H, d), 8.92 (2H, d)
62	2-([1,1'-biphenyl]-4-yl)-2,4-dihydro-3-hydroxy-4-methyl-5*H*--pyrazolo[4,3-*c*]isoquinolin-5--one	241–244	368 $(M+H)^+$	3.83 (3H, s), 7.39 (1H, m), 7.50 (2H, t), 7.75 (3H, m), 7.91 (3H, m), 8.05 (3H, m), 8.38 (1H, d)
63	2,4-Dihydro-3-hydroxy-4--methyl-2-(4-trifluoromethyl-phenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one	>250	360 $(M+H)^+$	3.81 (3H, s), 7.77 (1H, t), 7.94 (3H, m), 8.05 (1H, d), 8.18 (2H, d), 8.37 (1H, d), 11.37 (1H, s)
64	2-(6-Chloro-3-pyridyl)-2,4-dihydro-3-hydroxy-4-methyl--5*H*-pyrazolo[4,3-*c*]isoquinolin--5-one	>250	327/329 $(M+H)^+$	3.79 (3H, s), 7.73 (1H, d), 7.76 (1H, t), 7.92 (1H, t), 8.02 (1H, d), 8.38 (2H, m), 8.97 (1H, d)

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
65	2,4-Dihydro-3-hydroxy-2-(4--iodophenyl)-4-methyl-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one	>250	418 $(M+H)^+$	3.80 (3H, s), 7.74 (3H, m), 7.89 (3H, m), 8.02 (1H, d), 8.36 (1H, d)
66	2,4-Dihydro-3-hydroxy-4-(4--methoxyphenylmethyl)-2-(4--trifluoromethylphenyl)-5*H*--pyrazolo[4,3-*c*]isoquinolin-5--one	>230 dec.	466 $(M+H)^+$	3.68 (3H, s), 5.59 (2H, s), 6.83 (2H, d), 7.40 (2H, d), 7.75 (1H, t), 7.90 (3H, m), 8.07 (1H, d), 8.20 (2H, d), 8.38 (1H, d), 11.50 (1H, s)
67	2,4-Dihydro-3-hydroxy-4-(1--methylethyl)-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo-[4,3-*c*]isoquinolin-5-one	228–230 dec.	388 $(M+H)^+$	1.59 (6H, d), 5.85 (1H, brs), 7.76 (1H, t), 7.92 (3H, d), 8.04 (1H, d), 8.18 (2H, d), 8.36 (1H, d)
68	2,4-Dihydro-3-hydroxy-4--methyl-2-[4-(1-methylethyl)-phenyl]-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one	238–240	334 $(M+H)^+$	1.25 (6H, d), 2.96 (1H, hept), 3.81 (3H, s), 7.42 (2H, d), 7.72 (1H, t), 7.78 (2H, d), 7.89 (1H, t), 8.01 (1H, d), 8.36 (1H, d)

Example 69

2,4-Dihydro-3-hydroxy-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin--5-one

Trifluoroacetic acid (4 ml) was added to 2,4-dihydro-3-hydroxy-4-(methoxyphenylmethyl)--2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one (example 66) (425 mg) and the mixture was heated at reflux for 12 hours. After cooling to room temperature the solvent was removed and the resultant residue was recrystallised from methanol/water to give a yellow solid, which was further purified by trituration with isohexane to give the title compound (150 mg). m.p. >200 °C.

MS (APCI) 346 ($(M+H)^+$).

^{1}H NMR (d_6-DMSO) δ 7.76 (1H, t), 7.92 (3H, m), 8.02 (1H, d), 8.18 (2H, d), 8.34 (1H, d), 11.20 (1H, s)

The following examples were prepared analogously to example 69:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
70	2,4-Dihydro-3-hydroxy-2-[4--(1-methylethyl)phenyl]-5*H*--pyrazolo[4,3-*c*]isoquinolin-5--one	>250°	320 $(M+H)^+$	1.24 (6H, d), 2.95 (1H, m), 7.40 (2H, d), 7.70 (1H, t), 7.78 (2H, d), 7.88 (1H, t), 7.99 (1H, d), 8.32 (1H, d), 11.00 (1H, s)
71	2,4-Dihydro-3-hydroxy-2--([1,1'-biphenyl]-4-yl)-5*H*--pyrazolo[4,3-*c*]isoquinolin--5-one	275 dec.	354 $(M+H)^+$	7.39 (1H, t), 7.50 (2H, t), 7.74 (3H, d), 7.87 (3H, m), 8.01 (3H, m), 8.34 (1H, d), 11.13 (1H, s), 11.76 (1H, s)

Example 72

2-(4-Chlorophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-5-methyl-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt

A 3M solution of methylmagnesium bromide in diethyl ether (2.0 ml) was added dropwise to an ice cooled suspension of 2-(4-chlorophenyl)-3-hydroxy-4-[(4-methoxyphenyl)-methyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt (Ex. 22) (0.5 g) and copper(I) bromide (17 mg) in dry tetrahydrofuran (20 ml). The mixture was stirred cold for 1 hour before saturated aqueous ammonium chloride and ethyl acetate were added. This mixture was stirred at room temperature for 16 hours then the aqueous phase was extracted with ethyl acetate (thrice). The organic phase was washed with brine, dried over sodium sulphate, filtered and evaporated. The solid residue was purified by column chromatography (99:1 dichloromethane : methanol) to give a purple solid (0.38 g). A sample (0.1 g) was recrystallised from ethanol to give the title compound (31 mg).

m.p. 212–216 °C

MS (APCI) 430, 432 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) δ 2.88 (3H, s), 3.71 (3H, s), 6.50 (2H, br s), 6.93 (2H, d), 7.32 (2H, d), 7.51 (2H, d), 7.76 (1H, t), 7.98 (1H, t), 8.32 (1H, d), 8.43 (3H, m).

Example 73

2-(4-Chlorophenyl)-5-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

2-(4-Chlorophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-5-methyl-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt (0.29 g) was dissolved in trifluoroacetic acid (10 ml) and heated under reflux in a nitrogen atmosphere for 2 hours. On cooling to room temperature the solvent was evaporated and the residue was co-evaporated with toluene

(thrice). Purification by column chromatography (20:1 dichloromethane : methanol) followed by trituration with methanol gave the title compound as an orange solid (0.07 g). m.p. >250 °C

MS (APCI) 310, 312 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) δ 2.77 (3H, s), 7.47 (2H, d), 7.68 (1H, t), 7.77 (1H, t), 8.10 (1H, d), 8.25 (1H, d), 8.31 (2H, d).

The following examples were prepared following the method of example 72:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
74	4-Cyclopropyl-3-hydroxy-5--methyl-2-(4-trifluoromethyl-phenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt	>250	384 $(M+H)^+$	1.32 (2H, m), 1.48 (2H, m), 3.07 (3H, s), 4.04 (1H, m), 7.76 (3H, m), 7.95 (1H, t), 8.36 (2H, m), 8.62 (2H, d)
75	3-Hydroxy-4-(2-methoxy-ethyl)-5-methyl-2-[(4-tri-fluoromethyl)phenyl]-2*H*-pyr-azolo [4,3-*c*]isoquinolinium hydroxide, inner salt	202–204	402 $(M+H)^+$	3.00 (3H, s), 3.29 (3H, s), 4.08 (2H, t), 5.37 (2H, br s), 7.68 (3H, m), 7.88 (1H, t), 8.10 (1H, d), 8.56 (3H, m)

Example 76

2-(4-Chlorophenyl)-3-hydroxy-4,5-dimethyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt.

2-(4-Chlorophenyl)-2,4-dihydro-3-hydroxy-4-methylpyrazolo[4,3-*c*]isoquinolin-5-one (0.48 g) (Example 6) was suspended in dry 1,2-dimethoxyethane (50 ml). A solution of methylmagnesium bromide (3 ml of 3M solution in ether) was added and the mixture was heated under reflux for 0.75 h. Further methylmagnesium bromide (1 ml) was added and heating was continued for 3 h. The reaction was allowed to cool to ambient temperature and was then quenched by the slow addition of dilute hydrochloric acid. The mixture was basified with aqueous sodium bicarbonate solution and extracted with ethyl acetate (thrice). The organic phase was washed with brine, dried over magnesium sulfate, filtered and evaporated. Purification of the residue by chromatography (silica, 97:3–95:5 dichloro-methane : methanol) gave a red solid which was triturated with ether to give the title compound (0.060 g). m.p. >250 °C.

MS (APCI) 324/326 ($(M+H)^+$).

^{1}H NMR (d_6-DMSO) δ 2.90 (3H, s), 4.63 (3H, s), 7.49 (2H, d), 7.77 (1H, t), 7.95 (1H, t), 8.39 (4H, m).

The following examples were prepared following the method of example 76:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
77	5-Ethyl-3-hydroxy-4-methyl--2-(4-trifluoromethylphenyl)--2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt.	>250	372 $(M+H)^+$	1.45 (3H, t), 3.32 (2H, q), 4.78 (3H, s), 7.68 (3H, m), 7.88 (1H, td), 8.03 (1H, d), 8.54 (2H, d), 8.58 (1H, dd)
78	3-Hydroxy-5-methyl-4-(1--methylethyl)-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	205–210	386 $(M+H)^+$	1.76 & 1.90 (6H, 2 x m, rotamers), 3.07 (3H, s), 5.42 & 7.40 (1H, 2 x br, rotamers) 7.77 (3H, m), 7.97 (1H, t), 8.41 (2H, m), 8.62 (2H, m).
79	4-Methyl-5-(1-methylethyl)--3-hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	236–238	386 $(M+H)^+$	1.61 (6H, d), 4.05 (1H, br), 4.75 (3H, s), 7.76 (1H, t), 7.80 (2H, d), 7.94 (1H, t), 8.43 (1H, dd), 8.52 (1H, d), 8.60 (2H, d)
80	3-Hydroxy-4,5-dimethyl-2-(4--trifluoromethylphenyl)-2*H*--pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	358 $(M+H)^+$	2.87 (3H, s), 4.72 (3H, s), 7.66 (3H, m), 7.86 (1H, t), 8.01 (1H, d), 8.53 (3H, m)

Example 81

5-Chloro-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

Phosphorous oxychloride (5 ml) was added to 2,4-dihydro-3-hydroxy-4-(methoxyphenyl-methyl)-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one (example 66) (350 mg) and heated to reflux for 1 hour. After cooling to room temperature the solvent was removed and the residue was purified by column chromatography, eluting with isohexane : ethyl acetate : acetic acid (80:20:2) followed by trituration with acetonitrile to give the title compound (25 mg). m.p. >250 °C dec.

MS (APCI) 364/366 ($(M+H)^+$).

^{1}H NMR (d_6-DMSO) δ 7.96 (5H, m), 8.07 (1H, t), 8.25 (1H, d), 8.43 (1H, d)

Example 82

3a,4-Dihydro-3a-hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin--3,5-dione

Ceric ammonium nitrate (700 mg) was added to a suspension of 2,4-dihydro-3-hydroxy--4-(methoxyphenylmethyl)-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin--5-one (example 66) (200 mg) in acetonitrile (4 ml) and water (1 ml) at room temperature. After 2 hours the mixture was absorbed onto silica gel and purified by column chromatography, eluting with isohexane : propan-2-ol (9:1), and then HPLC, eluting with isohexane : ethyl acetate (4:1), to give the title compound (50 mg). m.p. 175–185 °C
MS (ESI) 360 $(M-H)^-$
^{1}H NMR (d_6-DMSO) δ 7.7–8.0 (5H, m), 8.08–8.12 (4H, m), 9.78 (1H, s).

Example 83

2,4-Dihydro-3-methoxy-4-methyl-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one.

2,4-Dihydro-3-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one (0.2 g) (Example 63) in dry dimethylformamide (5 ml) was added dropwise to a stirred suspension of oil-free sodium hydride (from 0.022 g 60% dispersion) in dry dimethylformamide (1 ml) at 0 °C. After 0.5 h methyl iodide (0.038 ml) was added. Stirring was continued for 16 h. The mixture was diluted with water, acidified with dilute hydrochloric acid and extracted with ethyl acetate (thrice). The organic phase was washed with brine (seven times) then dried over magnesium sulfate, filtered and concentrated. Purification by chromatography (25:75–50:50 ethyl acetate : dichloromethane then 30:70 ethyl acetate : isohexane) gave the title compound as a colourless solid (0.015 g).
m.p. 163–164 °C
MS (APCI) 374 $((M+H)^+)$
^{1}H NMR ($CDCl_3$) δ 3.78 (3H, s), 3.83 (3H, s), 7.60 (1H, td), 7.74 (1H, td), 7.80 (2H, d), 8.04 (2H, d), 8.27 (1H, dd), 8.48 (1H, dd).

Example 84

2-(4-Chlorophenyl)-4-{2-(*N*,*N*-dimethylamino)ethyl}-3-hydroxy-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt

2-(4-Chlorophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol (0.3 g) was added to a stirred suspension of oil-free sodium hydride (from 81 mg 60% dispersion) in dry dimethylformamide (5 ml) under a nitrogen atmosphere. After 30 minutes, 2-dimethyl-

aminoethyl chloride hydrochloride (0.15 g) was added and the mixture was stirred at room temperature for 16 h. The mixture was diluted with water and extracted with ethyl acetate (thrice). The organic phase was washed with brine then dried over sodium sulphate, filtered and concentrated to give a purple solid. Purification by column chromatography (20:1 dichloromethane : ethanol), followed by recrystallisation from 4:1 cyclohexane : ethyl acetate gave the title compound as a red solid (125 mg). m.p. 173–174 °C.
MS (APCI) 367, 369 ($(M+H)^+$).
^{1}H NMR (d_6-DMSO) δ 2.32 (6H, s), 3.02 (2H, t), 5.03 (2H, t), 7.4 (2H, d), 7.65 (1H, t), 7.85 (3H, m), 8.30 (2H, d), 8.50 (1H, d).

Example 85

3-Hydroxy-4-methyl-2-(4-methylsulfinylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt

3-Hydroxy-4-methyl-2-(4-methylthiophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt (0.10 g) (example 41) was dissolved in dichloromethane (15 ml) and cooled to -78 °C. 3-Chloroperbenzoic acid (0.055 g) was added and the mixture was stirred for 10 minutes before being poured into aqueous sodium metabisulfite and extracted with ethyl acetate (thrice). The combined extracts were shaken with aqueous sodium bicarbonate, dried with sodium sulfate and evaporated to give a residue which was purified by column chromatography (3:2 ethyl acetate : methanol) to give the title compound as a red powder (0.012 g). m.p. >230 °C.
MS(APCI): 338($(M+H)^+$).
^{1}H NMR (d_6-DMSO): δ 2.77 (3H, s), 4.52 (3H, s), 7.80 (3H, m), 7.96 (1H, t), 8.13 (1H, d), 8.37 (1H, d), 8.57 (2H, d), 8.64 (1H, s).

Example 86

2-(4-Chlorophenyl)-3-hydroxy-4-[2-(methylsulfinyl)ethyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt

3-Chloroperbenzoic acid (0.86 g) was dissolved in dichloromethane (20 ml). 6 ml of the resulting solution was added dropwise to a solution of 2-(4-chlorophenyl)-3-hydroxy--4-[2-(methylthio)ethyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt (example 46) (0.43 g) in dichloromethane (20 ml) at -78 °C. After 30 min aqueous sodium metabisulfite was added, and the reaction mixture was then partitioned between water and dichloromethane. The organic layer was washed with aqueous sodium hydroxide and then dried (magnesium sulfate), filtered, and evaporated. The residue was subjected to chromatography using methanol (2–6% by volume) in dichloromethane as the eluant to

give a purple solid (0.46 g).
m.p. 228–230 °C
MS (APCI+) 386, 388 ($(M+H)^+$)
^{1}H NMR (d_6-DMSO) δ 2.69 (3H, s), 3.47 (1H, m), 3.64 (1H, m), 5.11 (1H, m), 5.34 (1H, m), 7.50 (2H, m), 7.79 (1H, m), 7.99 (1H, m), 8.17 (1H, d), 8.38 (3H, m), 8.83 (1H, s).

Example 87

3-Hydroxy-4-[2-(methylsulfinyl)ethyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt

Prepared from 3-Hydroxy-4-[2-(methylthio)ethyl]-2-(4-trifluoromethylphenyl)-2*H*--pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt (example 47) following the method of example 86 to give the title compound as a purple solid. m.p. 241–243 °C.
MS (APCI+) 420 ($(M+H)^+$).
^{1}H NMR (d_6-DMSO) δ 2.70 (3H, s), 3.47 (1H, m), 3.64 (1H, m), 5.11 (1H, m), 5.36 (1H, m), 7.81 (3H, m), 8.01 (1H, m), 8.19 (1H, d), 8.38 (1H, d), 8.60 (2H, d), 8.86 (1H, s).

Example 88

5-[2-(4-Methoxyphenyl)ethyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol, sodium salt

Methylmagnesium bromide (3M in ether, 8.6 ml) was added slowly to a stirred suspension of 2,4-dihydro-3-hydroxy-4-(4-methoxyphenylmethyl)-2-(4-trifluoromethylphenyl)-5*H*--pyrazolo[4,3-*c*]isoquinolin-5-one (example 66) (500 mg) and copper (I) bromide (15 mg) in 1,2-dimethoxyethane (50 ml) and then heated at 100 °C for 24 hours. After being allowed to cool to room temperature the mixture was poured onto cold dilute hydrochloric acid and then basified with sodium hydrogen carbonate and sodium hydroxide. The aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solution followed by purification by column chromatography eluting successively with isohexane : ethyl acetate (1:1), ethyl acetate and ethyl acetate : methanol (9:1), gave the title compound as a red solid (90 mg). m.p. >200 °C dec.
MS (APCI) 464 ($(M+H)^+$)
^{1}H NMR (d_6-DMSO/TFA) δ 3.08 (2H, t), 3.59 (2H, t), 3.73 (3H, s), 6.87 (2H, d), 7.25 (2H, d), 7.92 (3H, m), 8.05 (1H, t), 8.33 (2H, d), 8.40 (1H, d), 8.50 (1H, d), 12.05 (TFA/water/1H).

Example 89

9-Fluoro-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt

(a) 2,6 Difluoro-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide

A solution of 2,6 difluorobenzoyl chloride (20 g) in dry dichloromethane (100 ml) was added dropwise to an ice cooled solution of 2-amino-2-methylpropanol (20.2 g) in dry dichloromethane (150 ml) under an atmosphere of nitrogen whilst maintaining the temperature below 5 °C. After addition was complete the ice bath was removed and stirring was continued a further 16 hours at room temperature. The organic phase was diluted with water and separated. The aqueous phase was then extracted with dichloromethane (twice) The combined organic phase was washed with brine, dried over sodium sulfate, filtered and then evaporated. Trituration with hexane gave the subtitle compound (24.65 g).

MS (APCI) 230 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$): δ 1.41 (6H, s), 3.70 (2H, d), 3.95 (1H, t), 6.00 (1H, br s), 6.95 (2H, m), 7.38 (1H, m).

(b) 2-(2,6-Difluorophenyl)-4,5-dihydro-4,4-dimethyloxazole

Thionyl chloride (12.6 ml) was added dropwise to an ice cooled solution of 2,6-difluoro--*N*-(2-hydroxy-1,1-dimethylethyl)benzamide (24.65 g) in dry dichloromethane (100 ml) under an atmosphere of nitrogen. After the addition the ice bath was removed and stirring was continued for 1 hour at room temperature. The solvent was then evaporated and the residue was triturated with diethyl ether. The resultant solid was dissolved in the minimum amount of water (80 ml) and then basified with sodium hydroxide pellets. The basic phase was then extracted with ethyl acetate (thrice). The organic extracts were combined and then washed with brine, dried over sodium sulfate, filtered and evaporated to give an oil which was purified by column chromatography (4:1 hexane : ethyl acetate) to give the subtitle compound (20.86 g).

MS (EI) 211 (M^+).

^{1}H NMR ($CDCl_3$): δ 1.42 (6H, s), 4.14 (2H, s), 6.95 (2H, m), 7.40 (1H, m).

(c) 4,5-Dihydro-2-(2-fluoro-6-methylphenyl)-4,4-dimethyloxazole

A 3M solution of methylmagnesium chloride in tetrahydrofuran (86 ml) was added dropwise to a solution 2-(2,6-difluorophenyl)-4,5-dihydro-4,4-dimethyloxazole (18.23 g) in dry tetrahydrofuran (60 ml) at 0 °C under a nitrogen atmosphere. The solution was stirred at 0 °C for 1 hour and then allowed to warm to room temperature over 16 hours. Saturated

ammonium chloride solution was added carefully to the reaction mixture which was then extracted with ethyl acetate (thrice). The organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to give the subtitle compound as a pale yellow oil (18.18 g).

MS (APCI) 208 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$): δ 1.42 (6H, s), 2.40 (3H, s), 4.12 (2H, s), 6.93 (1H, t), 7.00 (1H, d), 7.26 (1H, m).

(d) 2-Fluoro-6-methylbenzoic acid

4,5-Dihydro-2-(2-fluoro-6-methylphenyl)-4,4-dimethyloxazole (18.18 g) and excess iodomethane (20 ml) were heated under reflux in acetonitrile (150 ml) for 4 h and then allowed to cool to room temperature. The solvent was evaporated and the solid residue was triturated with diethyl ether. The resultant solid was then dissolved in a mixture of methanol (80 ml) and 10% sodium hydroxide solution (80 ml) and heated under reflux for 4 hours. The reaction mixture was allowed to cool to room temperature and then the methanol was evaporated. The aqueous residues were washed with ethyl acetate (thrice) and then acidified with dilute hydrochloric acid to pH 1. The acidic phase was extracted with ethyl acetate (thrice). The organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to give 2-fluoro-6-methylbenzoic acid (10.85 g). A sample (0.27 g) was recrystallised from 4:1 hexane : ethyl acetate to give the subtitle compound (0.15 g). m.p. 123–124 °C.

MS (EI) 154 (M^+).

^{1}H NMR ($CDCl_3$) δ 2.52 (3H, s), 7.02 (2H, m), 7.35 (1H, m).

(e) Methyl 2-fluoro-6-methylbenzoate

Cesium carbonate (16 g) and iodomethane (4.6 ml) were added to a stirred solution of 2-fluoro-6-methylbenzoic acid (3.78 g) in dry dimethylformamide (25 ml) under an atmosphere of nitrogen. Stirring was continued at room temperature for 16 hours and then the reaction mixture was diluted with water and extracted with ethyl acetate (thrice). The organic phase was washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, and brine, then dried over sodium sulfate, filtered and evaporated to give the subtitle compound as a yellow oil (4.07 g).

MS (EI) 168 (M^+)

^{1}H NMR ($CDCl_3$).δ 2.40 (3H, s), 3.94 (3H, s), 6.94 (1H, t), 7.01 (1H, d), 7.30 (1H, m).

(f) Methyl 2-(bromomethyl)-6-fluorobenzoate

A suspension of methyl 2-fluoro-6-methylbenzoate (35.53 g), *N*-bromosuccinimide (37.6 g) and azobis(isobutyronitrile) (2 g) in dry dichloromethane (150 ml) was irradiated (100W halogen lamp) under an atmosphere of nitrogen for 4 hours. The resultant solution was poured onto 10% sodium hydroxide solution and extracted with dichloromethane (thrice). The organic phase was washed with brine, dried over sodium sulfate, filtered and evaporated to give a mixture of subtitle compound and starting material (52.33 g) as a yellow oil.

MS (EI) 246/248 (M^+)

^{1}H NMR ($CDCl_3$) δ 3.99 (3H, s), 4.66 (2H, s), 7.06 (1H, t), 7.23 (1H, d), 7.40 (1H, m).

(g) Methyl 2-fluoro-6-{[(2-methoxy-2-oxoethyl)-(4-methoxyphenylmethyl)amino]-methyl}benzoate

N-(4-Methoxyphenylmethyl)glycine methyl ester (10.2 g) was added dropwise to a stirred solution of methyl 2-(bromomethyl)-6-fluorobenzoate (11 g) and triethylamine (6.8 ml) in dry diethyl ether (50 ml). The mixture was heated under reflux in a nitrogen atmosphere for 16 hours. The reaction mixture was allowed to cool and was then diluted with water and extracted with ethyl acetate (thrice). The organic phase was washed with brine, dried over sodium sulfate, filtered and then evaporated. The residue was purified by column chromatography (20:1 hexane : ethyl acetate) to give the subtitle compound as a colourless oil (8.82 g).

MS (APCI) 376 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$): δ 3.21 (2H, s), 3.67 (3H, s), 3.68 (2H, s), 3.78 (3H, s), 3.88 (3H, s), 4.01 (2H, s), 6.82 (2H, d), 7.05 (1H, t), 7.18 (3H, m), 7.35 (1H, m).

(h) Methyl 5-fluoro-1,2,3,4-tetrahydro-2-(4-methoxyphenylmethyl)-4-oxo-3-iso-quinolinecarboxylate

A solution of methyl 2-fluoro-6-{[(2-methoxy-2-oxoethyl)-(4-methoxyphenylmethyl)-amino]methyl}benzoate (8.82 g) in dry toluene (50 ml) was added dropwise to a suspension of sodium hydride (1.32 g of a 60% dispersion, freed from oil) and *tert*-butyl alcohol (1 ml) in dry toluene (100 ml) heated under reflux in a nitrogen atmosphere. Heating was continued a further 12 hours then the reaction mixture was allowed to cool to room temperature. The mixture was then poured onto saturated aqueous ammonium chloride solution and extracted with ethyl acetate (thrice). The organic phase was washed with brine, dried over sodium sulfate, filtered and evaporated to give the subtitle compound (7.96 g). MS (APCI) 344 ($(M+H)^+$).

^{1}H NMR ($CDCl_3$): δ 3.60 (2H, s), 3.81 (3H, s), 3.89 (2H, s), 3.92 (3H, s), 6.86 (3H, m), .7.05 (1H, m), 7.22 (2H, m), 7.38 (1H, m), 11.83 (1H, s).

(i) 9-Fluoro-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-trifluoromethylphenyl)-2*H*--pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt

Methyl 5-fluoro-1,2,3,4-tetrahydro-2-(4-methoxyphenylmethyl)-4-oxo-3-isoquinolinecarboxylate (1.0 g), 4-trifluoromethylphenylhydrazine (1.03 g) and p-toluene sulfonic acid (20 mg) were fused together at 150 °C under a nitrogen atmosphere for 15 minutes. Xylene (20 ml) was then added and heating was continued a further 2 hours. On cooling to room temperature the solvent was evaporated and the solid residue was purified by column chromatography (99:1 dichloromethane : methanol) to give the title compound as purple needles (0.425 g).

MS (APCI) 468 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) δ 3.72 (3H, s), 6.10 (2H, s), 6.96 (2H, d), 7.70 (2H, d), 7.80 (4H, m), 8.00 (1H, dd), 8.59 (2H, d), 8.98 (1H, s).

Example 90

9-Fluoro-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol

9-Fluoro-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt (0.43 g) was dissolved in trifluoroacetic acid (5 ml) and heated under reflux in a nitrogen atmosphere for 16 hours. After being cooled to room temperature the solvent was evaporated and the residue was co-evaporated with toluene (thrice). The residue was triturated successively with methanol and then diethyl ether and finally recrystallised from ethyl acetate to give the title compound as a red solid (0.08 g). m.p. >250 °C.

MS (APCI) 348 ($(M+H)^+$).

^{1}H NMR (d_6-DMSO) δ 7.86 (2H, m), 7.95 (2H, d), 8.14 (1H, d), 8.24 (2H, br d), 9.09 (1H, br s), 11.85 (1H, br s).

The following compounds were made by methods analogous to example 90:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
91	2-(4-Chlorophenyl)-7-fluoro--3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	328/330 $(M+H)^+$	4.51 (3H, s), 7.46 (2H, d), 7.77 (1H, td), 7.87 (1H, dd), 8.36 (3H, m), 8.45 (1H, s)

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
92	7-Fluoro-3-hydroxy-4-methyl--2-(4-trifluoromethylphenyl)--2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	362 $(M+H)^+$	4.51 (3H, s), 7.75 (2H, d), 7.80 (1H, m), 7.87 (1H, dd), 8.38 (1H, dd), 8.47 (1H, s), 8.54 (2H, d)
93	2-(4-Chlorophenyl)-4-cyclopropyl-9-fluoro-3-hydroxy--2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>214–217	354/ 356 $(M+H)^+$	1.35 (2H, m), 1.54 (2H, m), 5.11 (1H, m), 7.51 (2H, d), 7.75 (2H, m), 7.95 (1H, dd), 8.38 (2H, d), 8.63 (1H, s).
94	4-Cyclopropyl-9-fluoro-3--hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	388 $(M+H)^+$	1.36 (2H, m), 1.55 (2H, m), 5.06 (1H, m), 7.77 (4H, m), 7.97 (1H, m), 8.58 (2H, d), 8.66 (1H, s)
95	2-(4-Chlorophenyl)-9-fluoro--3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	328/ 330 $(M+H)^+$	4.51 (3H, s), 7.51 (2H, d), 7.76 (2H, m), 7.91 (1H, m), 8.35 (2H, d), 8.65 (1H, s)
96	2-(4-Chlorophenyl)-9-fluoro--3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	434/ 436 $(M+H)^+$	3.72 (3H, s), 6.10 (2H, s), 6.95 (2H, d), 7.54 (2H, d), 7.70 (2H, d), 7.77 (2H, m), 7.97 (1H, m), 8.39 (2H, d), 8.96 (1H, s)
97	9-Fluoro-3-hydroxy-4-methyl--(4-trifluoromethylphenyl)--2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	>250	362 $(M+H)^+$	4.51 (3H, s), 7.77 (4H, m), 7.93 (1H, m), 8.56 (2H, d), 8.68 (1H, s)

The following compounds (examples 98–100) were prepared following the methods of example 2:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
98	2-(4-Chlorophenyl)-9--fluoro-2*H*-pyrazolo-[4,3-*c*]isoquinolin-3-ol	>250	314/316 $(M+H)^+$	7.63 (2H, d), 7.82 (2H, br m), 8.01 (2H, d), 8.11 (1H, br d), 9.05 (1H, br s), 11.80 (1H, br s)
99	7-Fluoro-2-(4-trifluoro-methylphenyl)-2*H*-pyr-azolo[4,3-*c*]isoquinolin-3--ol	>250	348 $(M+H)^+$	7.93 (3H, d), 8.14 (1H, d), 8.28 (2H, d), 8.41 (1H, dd), 9.02 (1H, br s)
100	2-(4-Chlorophenyl)-7--fluoro-2*H*-pyrazolo-[4,3-*c*]isoquinolin-3-ol	>250	314/316	7.63 (2H, d), 7.91 (1H, br t), 8.05 (2H, d), 8.13 (1H, d), 8.40 (1H, dd), 9.00 (1H, br s), 12.00 (1H, br s)

The following compounds were prepared following the method of example 69:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
101	9-Fluoro-3-hydroxy-4-[(4-meth-oxyphenyl)methyl]-5-methyl-2--(4-trifluoromethylphenyl)-2*H*--pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	225–227	482 $(M+H)^+$	2.86 (3H, s), 3.73 (3H, s), 6.53 (2H, s), 6.92 (2H, d), 7.30 (2H, d), 7.74 (4H, m), 8.11 (1H, d), 8.58 (2H, d)
102	2-(4-Chlorophenyl)-9-fluoro-3--hydroxy-4-[(4-methoxy-phenyl)methyl]-5-methyl-2*H*--pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt	222–223	448/450 $(M+H)^+$	2.85 (3H, s), 3.73 (3H, s), 6.53 (2H, s), 6.91 (2H, d), 7.29 (2H, d), 7.44 (2H, d), 7.70 (2H, m), 8.08 (1H, d), 8.37 (2H, d)

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The following compounds were prepared by the method of example 2:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
103	9-Fluoro-5-methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol	>250	362 $(M+H)^+$	2.80 (3H, s), 7.79 (2H, m), 7.88 (2H, d), 8.10 (1H, d), 8.32 (2H, d)
104	2-(4-chlorophenyl)-9-fluoro-5--methyl-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol	>250	328/330 $(M+H)^+$	2.89 (3H, s), 7.58 (2H, d), 7.79 (2H, br m), 8.08 (3H, br m)

Example 105

2,4-Dihydro-3-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinoline-5-thione.

A solution of 2,4-dihydro-3-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo-[4,3-*c*]isoquinolin-5-one (example 63) (0.25 g) and Lawesson's reagent (0.7 g) in dioxane (20 ml) was stirred and heated under reflux for 18 hrs. The resulting mixture was cooled and absorbed onto silica gel. Purification by chromatography (1:99–3:97 methanol : dichloromethane) gave the title compound which was crystallised from ethanol to afford a yellow solid (0.075 g). m.p. 255–259 °C.

MS (APCI) 376 ($(M+H)^+$).

^{1}H NMR (D_2O/NaOD) δ 8.47 (1H, d), 7.71 (2H, d), 7.60 (3H, m), 7.34 (1H, t), 7.22 (1H, t), 4.08 (3H, s).

Example 106

3-Hydroxy-4-methyl-5-methylthio-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt.

A solution of 2,4-dihydro-3-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo-[4,3-*c*]isoquinoline-5-thione (0.46 g) (example 105) and iodomethane (0.095 ml) in acetone (50 ml) was stirred and heated under reflux for 4 hr. Potassium carbonate (0.170 g) was added and the mixture was heated for a further 2 hr. The mixture was concentrated *in vacuo*. Purification of the residue by chromatography (2:98 methanol : dichloromethane) gave the title compound as a purple solid (0.375 g).

MS (APCI) 390 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 8.54 (4H, m), 7.86 (1H, t), 7.72 (3H, m), 4.98 (3H, s), 2.52 (3H, s).

Example 107

2-(4-Trifluoromethylphenyl)-2,4-dihydro-5-imino-4-methyl-5*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol.

A suspension of 3-hydroxy-4-methyl-5-methylthio-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt (0.013 g) (example 106) in ethanol (7 ml) and ammonia solution (0.880 specific gravity; 15 ml) was stirred at 20 °C for 24 hr. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by chromatography (5:95–10:90 methanol : dichloromethane) gave the title compound as an orange solid (0.043 g). m.p. 253–255 °C.

MS (APCI) 717 ($(2M+H)^+$), 359 ($(M+H)^+$).

^{1}H NMR (d_6-DMSO) δ 8.60 (2H, d), 8.46 (1H, d), 8.29 (3H, m), 7.90 (1H, t), 7.71 (3H, m), 4.19 (3H, s).

Example 108

3-Hydroxy-4-(4-methoxyphenyl)methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[3,4-*f*][1,7]naphthyridinium hydroxide, inner salt

(a) Methyl 2-(bromomethyl)nicotinate

Methyl 2-methylnicotinate (10.0 g) and *N*-bromosuccinimide (14.9 g) were combined in 1,2-dichloroethane (80 ml). Acetic acid (3.8 ml) was added followed by 2,2'-azobis-(2-methylpropionitrile) (1.0 g) and the mixture was heated to reflux whilst being irradiated with a 500W lamp. After 2 h the reaction was allowed to cool and then poured onto sodium bicarbonate solution. The organic phase was separated and was washed with brine twice, then dried, filtered and evaporated to an oil (18.2 g) which was used immediately for the next step.

(b) *N*-[(4-methoxyphenyl)methyl]-*N*-[(3-methoxycarbonyl-2-pyridyl)methyl]glycine methyl ester

Prepared following the method of example 1 step (a) using methyl 2-(bromomethyl)-nicotinate (9.10 g), methyl *N*-(4-methoxyphenyl)methylglycine (10.2 g) and triethylamine (5.5 ml) in diethyl ether (100 ml) to give the subtitle compound (3.20 g)

MS (DESC SI) 358 (M^+)

^{1}H NMR (d_6-DMSO) 3.17 (s, 2H), 3.34 (s, 3H), 3.58 (s, 2H), 3.71 (s, 3H), 3.82 (s, 3H), 4.23 (s, 2H), 6.82 (d, 2H), 7.04 (d, 2H), 7.43 (dd, 1H), 8.03 (dd, 1H), 8.61 (dd, 1H)

(c) Methyl 7,8-dihydro-5-hydroxy-7-(4-methoxyphenyl)methyl[1,7]naphthyridine--6-carboxylate

Prepared following the method of example 1 step (b) using *N*-[(4-methoxyphenyl)methyl]--*N*-[(3-methoxycarbonyl-2-pyridyl)methyl]glycine methyl ester (1.00 g), sodium hydride (60% dispersion in oil) (160 mg), 2-methylpropan-2-ol (0.10 ml) and toluene (15 ml) to give the subtitle compound (790 mg).

MS (APCI) 327 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) 3.65–3.97 (m, 10H), 6.79 (m, 2H), 7.11–7.39 (m, 3H), 7.86–8.25 (m, 1H), 8.52–8.75 (m, 1H), 11.25 (s, 1H)

(d) 3-Hydroxy-4-(4-methoxyphenyl)methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[3,4-*f*][1,7]naphthyridinium hydroxide, inner salt

Prepared following the method of example 1 step [c] using methyl 7,8-dihydro-5-hydroxy--7-(4-methoxyphenyl)methyl-1,7-naphthyridine-6-carboxylate (200 mg), 4-trifluoromethylphenylhydrazine (1.00 g) and ethanol (3 ml) to give the title compound (21 mg).

m.p. 201–3 °C.

MS (APCI) 451 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) 3.72 (s, 3H), 6.13 (s, 2H), 6.96 (d, 2H), 7.76 (d, 2H), 7.84 (d, 2H), 7.88 (dd, 1H), 8.59 (d, 2H), 8.72 (dd, 1H), 9.00 (s, 1H), 9.05 (dd, 1H)

Example 109

2-(4-Trifluoromethylphenyl)-2*H*-pyrazolo[3,4-*f*][1,7]naphthyridin-3-ol

Prepared following the method of example 2 using 3-hydroxy-4-(4-methoxyphenyl)methyl--2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[3,4-*f*][1,7]naphthyridinium hydroxide, inner salt (135 mg) and trifluoroacetic acid (5 ml) to give the title compound (19 mg).

m.p. 239–41 °C (dec.)

MS (APCI) 331 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) 7.94 (d, 2H), 7.95 (m, 1H), 8.28 (d, 2H), 8.74 (d, 1H), 9.01 (br, 1H), 9.16 (d, 1H)

The following examples were prepared analogously to example 109 using methyl 2-(bromomethyl)nicotinate, sarcosine methyl ester and the appropriate hydrazine:

Ex.	Name	m.p./°C	MS	^{1}H NMR (d_6-DMSO) δ
110	3-Hydroxy-4-methyl-2-(4-trifluoro-methylphenyl)-2*H*-pyrazolo[3,4-*f*]-[1,7]naphthyridinium hydroxide, inner salt	>260	345 $(M+H)^+$	4.56 (s, 3H), 7.82 (d, 2H), 7.88 (dd, 1H), 8.56 (d, 2H), 8.70 (s, 1H), 8.73 (s, 1H), 9.05 (d, 1H)
111	2-(4-Chlorophenyl)-3-hydroxy--4-methyl-2*H*-pyrazolo[3,4-*f*][1,7]-naphthyridinium hydroxide, inner salt	>260	311/313 $(M+H)^+$	4.56 (s, 3H), 7.51 (d, 2H), 7.88 (dd, 1H), 8.35 (d, 2H), 8.68 (s, 1H), 8.70 (dd, 1H), 9.03 (dd, 1H)

Example 112

3-Hydroxy-4-methyl-5-(dimethylamino)-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide inner salt.

A solution of 3-hydroxy-4-methyl-5-methylthio-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt (0.39 g) (example 106) in acetone (10 ml) and 40% aqueous dimethylamine solution (2 ml) was stirred at 20 °C for 24 h. The mixture was concentrated *in vacuo*. Purification of the residue by chromatography (1:99–2.5:97.5 methanol : dichloromethane) gave the title compound as a red solid (0.129 g). m.p. 256–259 °C.

MS (APCI) 387 ($(M+H)^+$).

^{1}H NMR ($CDCl_3$) d 3.19 (6H, s), 4.52 (3H, s), 7.64 (3H, m), 7.84 (1H, td), 7.95 (1H, d), 8.54 (3H, d)

Example 113

3-Hydroxy-4-methyl-5-morpholinyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide inner salt.

A solution of 3-hydroxy-4-methyl-5-methylthio-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt (0.520 g) (example 106) in dry tetrahydrofuran (7 ml) and morpholine (2.3 ml) was heated to 70 °C for 12h and then at 95 °C for 2h. The mixture was concentrated *in vacuo*. Purification of the residue by chromatography (5:95 methanol : dichloromethane) gave the title compound as a red solid (0.165 g). m.p. 278–281 °C.

MS (APCI) 429 ($(M+H)^+$).

^{1}H NMR (d6-DMSO) d 3.49 (4H, m), 3.87 (4H, m), 4.49 (3H, s), 7.77 (2H, m), 7.94 (1H, t), 8.28 (1H, d), 8.38 (1H, d), 8.59 (2H, d).

Example 114

3-Hydroxy-4-methyl-5-piperazinyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide inner salt.

A solution of 3-hydroxy-4-methyl-5-methylthio-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt (0.29 g) (example 106) in toluene (20 ml) was added dropwise to a stirred solution of piperazine (1.28 g) in toluene (50 ml) heated at 110 °C. The resulting solution was stirred at 110 °C for 6h. then at room temperature for 16h. The mixture was concentrated *in vacuo*.. Purification of the residue by chromatography (5:95-10:90 methanol : dichloromethane) followed by crystallisation from ethanol gave the title compound as a red solid (0.107g). m.p. 260–262 °C.

MS (APCI) 428 ($(M+H)^+$).

^{1}H NMR (DMSO) d 2.96 (4H, m), 3.37 (4H, m), 4.44 (3H, s), 7.76 (3H, m), 7.93 (1H, t), 8.27 (1H, d), 8.37 (1H, d), 8.59 (2H, d).

Example 115

4,5-Dihydro-2-[4-(trifluoromethyl)phenyl]-2H-benz[g]indazol-3-ol

1-Oxotetrahydronaphthalene-2-carboxylic acid methyl ester (Mander, L.N and Sethi, S.P; Tetrahedron Lett. 1983, 24, 5425-8) (2.0g) and 4-trifluoromethylphenylhydrazine (3.47g) were heated in xylene (15ml) under reflux for 8h. The reaction mixture was allowed to cool and then the product was filtered. The solid was washed with diethyl ether, dried and recrystallised from toluene gave the title compound as colourless crystals. (1.45g). m.p. 189-190 °C.

MS (APCI) 331 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) d 2.67 (2H, m), 2.90 (2H, m), 7.29 (3H, m), 7.75 (1H, m), 7.84 (2H, d), 8.10 (2H, d), 11.70 (1H, s,br).

Example 116

4,5-Dihydro-2-(5-methyl-2-pyridinyl)-2H-benz[g]indazol-3-ol

1-Oxotetrahydronaphthalene-2-carboxylic acid methyl ester (2.18g) and 2-hydrazino-5-methylpyridine (2.85g) were heated together in xylene (15ml) under reflux for 6h. The reaction was allowed to cool and then the product was filtered and dried. Recrystallisation

from diethyl ether/isohexane gave the title compound as pale brown needles (0.69g). m.p. 112°C.

MS (APCI) 278 ($(M+H)^+$).

^{1}H NMR (d_6-DMSO) d 2.36 (3H, s), 2.73 (2H, t), 2.95 (2H, t), 7.29 (3H, m), 7.68 (1H, dd), 7.92 (1H, d), 7.94 (1H, m), 8.07 (1H, s), 12.73 (1H, s,br).

Example 117

2-[4-(Trifluoromethyl)phenyl]-2H-benz[g]indazol-3-ol

4,5-Dihydro-2-[4-(trifluoromethyl)phenyl]-2H-benz[g]indazol-3-ol (0.30g) and 10% palladium on charcoal (0.10g) were heated in dimethylacetamide (5ml) and cyclohexene (5ml) under reflux for 1h. the title compound (0.26g). m.p. >235 °C (dec)

MS (APCI) 329 ($(M+H)^+$)

^{1}H NMR (d_6-DMSO) d 7.70 (4H, m), 7.85 (2H, d), 8.07 (1H, m), 8.27 (2H, d), 8.30 (1H, m), 11.70 (1H, s, br).

Example 118

2-(5-Methyl-2-pyridinyl)-2H-benz[g]indazol-3-ol

4,5-Dihydro-2-(5-methyl-2-pyridinyl)-2H-benz[g]indazol-3-ol (0.40g) and 10% palladium on charcoal (0.20g) were heated in dimethylacetamide (15ml) and cyclohexene (15ml) under reflux for 8h. The mixture was allowed to cool to ambient temperature and then filtered. The filtrate was evaporated (100 °C /1mmHg) and the residue was recrystallised from ethyl acetate to give the title compound as pale orange crystals (0.12g). m.p. 214 °C.

MS (APCI) 276 ($(MH)^+$)

^{1}H NMR (d_6-DMSO) d 2.36 (3H, s), 7.52 (1H, d), 7.66 (3H, m), 7.82 (1H, dd), 8.02 (1H, d), 8.41 (1H, s, br), 8.53 (2H, m).

Pharmacological Data

Test A - Chronic graft-versus-host test

Pharmacological activity of the compounds of the invention may be demonstrated using the method of J. M. Doutrelepont *et al.* ([*Clin. Exp. Immunol.*, 1991, vol. **83**, 133–6; Inhibition of chronic graft-versus-host (c-GVH) disease in the mouse]. Test compound was administered to mice subcutaneously as a suspension in saline with TWEEN-80 every day for 21 days.

Test B - Inhibition of Eosinophilia

The effects of the compounds of the invention on inflammatory cells in mouse lungs was assessed by the following method, adapted from Brusselle *et al.*, *Clin. Exp. Allergy*, 1994, **24**, 73–80. The measurement of eosinophil peroxidase as a marker for eosinophil numbers was adapted from Cheng *et al.*, *J. Pharmacol. Exp. Ther.* 1993, **264**, 922–929.

Male Balb/c mice were sensitised to ovalbumin/$Al(OH)_3$ mixture.

14 days after sensitisation dosing with compound commenced. Compound was administered daily either orally or subcutaneously as a suspension or solution (depending on dose and compound solubility) in 5% TWEEN 80.

17 days after sensitisation and one hour after the fourth dose of compound, the mice were placed in Perspex chambers into which a solution of ovalbumin (2% w/v) was nebulised. The mice were allowed to inhale the ovalbumin for a period of 30-40 min. This challenge was repeated daily at the same time for a further 3 or 7 days.

In the case of the 4 day challenge, on the final day of dosing an additional challenge with ovalbumin was given 4 hours after the first.

The following day the animals were sacrificed and inhibition of the following parameters was measured by comparison to control animals:

(1) Increase in the numbers of inflammatory cells in the bronchioalveolar lavage, in particular eosinophils (after the 4 day dosing).

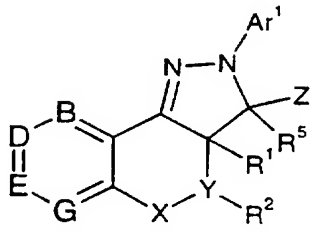
(2) Accumulation of eosinophils within lung tissue, as measured by the increase in eosinophil peroxidase activity in homogenised lung tissue (after the 8 day dosing).

(3) Increase in antibody titres (IgE, IgG1 and IgG2a) present in the serum obtained from whole blood (after the 8 day dosing).

Certain compounds of the invention show activities in the chronic graft versus host test and the inhibition of eosinophilia test with ED_{50}'s in the range of 0.1 - 10 mg/kg.

CLAIMS

1. A compound of formula I or a pharmaceutically acceptable derivative thereof for use as a pharmaceutical:



(I)

wherein:

- B, D, E and G each represent CH, CA or N provided that no more than one of B, D, E and G represents CA and no more than one of B, D, E and G represents N;
- X represents C=O, C=S, C=NR^{15}, CR^3R^6 or NR^4;
- Y represents N or N^+R^7 or CR^{18};
- Z represents OR^8 or O^-;
- R^1 represents OH or C_{1-6} alkyl, or with either R^2 or R^5 forms a bond;
- R^2 represents H, C_{1-6} alkyl (optionally substituted by phenyl, $COOR^9$, $NR^{10}R^{11}$, OR^{12} or F) or C_{3-7} cycloalkyl, or with either R^1, R^3 or R^4 forms a bond;
- R^3 represents H or a bond with R^2;
- R^4 represents C_{1-6} alkyl or a bond with R^2;
- R^5 represents a bond with R^1 or R^8;
- R^6 represents H, C_{1-6} alkyl (optionally substituted by phenyl), C_{3-7} cycloalkyl, phenyl, halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, cyano or $NR^{13}R^{14}$;
- R^7 represents C_{1-6} alkyl (optionally substituted by phenyl) or C_{3-7} cycloalkyl, either of which may be optionally substituted by halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, $NR^{16}R^{17}$, COOH, $COO(C_{1-6}$ alkyl) or cyano;
- or R^6 and R^7 together represent C_{3-5} alkylene, X and Y thereby forming a ring of 5–7 members;
- R^8 represents H, C_{1-6} alkyl or a bond with R^5;
- R^9, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17} and R^{18} independently represent C_{1-6} alkyl or H;

- R^{13} and R^{14} are independently C_{1-6} alkyl, H or together with the nitrogen atom to which they are attached form a 3-7 membered saturated ring optionally containing a further oxygen atom or a nitrogen atom optionally substituted by C_{1-6} alkyl;
- Ar^1 represents phenyl, pyridyl, pyrimidinyl, 2-benzothiazolyl, 2- or 3-quinolyl or 2-quinoxalinyl, all of which are optionally substituted by one or more substituents selected from halo, nitro, cyano, phenyl, phenylsulfonyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, COOH, $COO(C_{1-6}$ alkyl), C_{1-6} alkyl substituted by phenyl, or phenyl, in which any alkyl, alkoxy, alkylthio and alkylsulfinyl groups may optionally be substituted by fluoro; and
- A represents halo, cyano, amino, nitro, C_{1-6} alkyl or C_{1-6} alkoxy;

in which phenyl groups which are found in R^2, R^6, R^7 or as substituents on Ar^1 may be optionally substituted by C_{1-6} alkyl, halogen or C_{1-6} alkoxy;

with the provisos that:

(i) when X represents C=O, C=S or $C=NR^{15}$, then Y represents N;

(ii) when R^4 represents a bond with R^2, then Y represents N^+R^7;

(iii) when Y represents N^+R^7, then Z represents O^-, R^2 represents a bond with R^3 or R^4 and R^1 and R^5 form a bond;

(iv) when Y represents N, then Z represents OR^8;

(v) when R^1 represents OH, then X represents C=O, Y represents N, Z represents OR^8 and R^5 represents a bond with R^8;

(vi) when R^1 represents alkyl, then R^5 represents a bond with R^8, Y represents N, R^2 does not represent a bond, and X does not represent NR^4;

(vii) when R^1 represents a bond with R^2, then R^5 and R^8 form a bond, and if X represents NR^4 then R^4 represents alkyl;

(viii) when R^6 represents aryl, halogen, alkoxy, thioalkyl, then R^2 and R^3 form a bond;

(ix) when Y represents N or N^+R^7 and R^2 is substituted by any of $NR^{10}R^{11}$, OR^{12} or F, then the substituent and the ring nitrogen of Y may not be attached to the same carbon atom of R^2;

(x) when R^7 is substituted by any of $NR^{16}R^{17}$, OR^{12} or halogen then the substituent and the ring nitrogen of Y may not be attached to the same carbon atom of R^7;

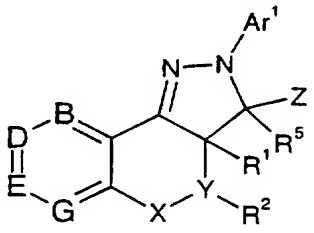
(xi) when one of B, D, E and G represents N, then X does not represent NR^4;

(xii) when Y represents CR^{18}, then X represents CR^3R^6;

with the further proviso that:

- when B, D, E and G all represent CH, X represents CHR^3, Y represents nitrogen, R^1 and R^5 form a bond, R^8 represents H and R^2 and R^3 together represent a bond, then Ar^1 does not represent 4-chlorophenyl, 4-fluorophenyl or 4-methoxyphenyl.

2. A compound of formula I:



(I)

wherein—

- B, D, E and G each represent CH, CA or N provided that no more than one of B, D, E and G represents CA and no more than one of B, D, E and G represents N;
- X represents C=O, C=S, $C=NR^{15}$, CR^3R^6 or NR^4;
- Y represents N or N^+R^7 or CR^{18};
- Z represents OR^8 or O^-;
- R^1 represents OH or C_{1-6} alkyl, or with either R^2 or R^5 forms a bond;
- R^2 represents H, C_{1-6} alkyl (optionally substituted by phenyl, $COOR^9$, $NR^{10}R^{11}$, OR^{12} or F) or C_{3-7} cycloalkyl, or with either R^1, R^3 or R^4 forms a bond;
- R^3 represents H or a bond with R^2;
- R^4 represents C_{1-6} alkyl or a bond with R^2;
- R^5 represents a bond with R^1 or R^8;
- R^6 represents H, C_{1-6} alkyl (optionally substituted by phenyl), C_{3-7} cycloalkyl, phenyl, halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, cyano or $NR^{13}R^{14}$;
- R^7 represents C_{1-6} alkyl (optionally substituted by phenyl) or C_{3-7} cycloalkyl, either of which may be optionally substituted by halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, $NR^{16}R^{17}$, COOH, $COO(C_{1-6}$ alkyl) or cyano;
- or R^6 and R^7 together represent C_{3-5} alkylene, X and Y thereby forming a ring of 5–7 members;
- R^8 represents H, C_{1-6} alkyl or a bond with R^5;
- R^9, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17} and R^{18} independently represent C_{1-6} alkyl or H;
- R^{13} and R^{14} are independently C_{1-6} alkyl, H or together with the nitrogen atom to which they are attached form a 3-7 membered saturated ring optionally

containing a further oxygen atom or a nitrogen atom optionally substituted by C_{1-6} alkyl;

- Ar^1 represents phenyl, pyridyl, pyrimidinyl, 2-benzothiazolyl, 2- or 3-quinolyl or 2-quinoxalinyl, all of which are optionally substituted by one or more substituents selected from halo, nitro, cyano, phenyl, phenylsulfonyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, COOH, $COO(C_{1-6}$ alkyl), C_{1-6} alkyl substituted by phenyl, or phenyl, in which any alkyl, alkoxy, alkylthio and alkylsulfinyl groups may optionally be substituted by fluoro; and
- A represents halo, cyano, amino, nitro, C_{1-6} alkyl or C_{1-6} alkoxy;

in which phenyl groups which are found in R^2, R^6, R^7 or as substituents on Ar^1 may be optionally substituted by C_{1-6} alkyl, halogen or C_{1-6} alkoxy;

with the provisos that—

(i) when X represents C=O, C=S or $C=NR^{15}$, then Y represents N;

(ii) when R^4 represents a bond with R^2, then Y represents N^+R^7;

(iii) when Y represents N^+R^7, then Z represents O^-, R^2 represents a bond with R^3 or R^4 and R^1 and R^5 form a bond;

(iv) when Y represents N, then Z represents OR^8;

(v) when R^1 represents OH, then X represents C=O, Y represents N, Z represents OR^8 and R^5 represents a bond with R^8;

(vi) when R^1 represents alkyl, then R^5 represents a bond with R^8, Y represents N, R^2 does not represent a bond, and X does not represent NR^4;

(vii) when R^1 represents a bond with R^2, then R^5 and R^8 form a bond, and if X represents NR^4 then R^4 represents alkyl;

(viii) when R^6 represents aryl, halogen, alkoxy, thioalkyl, then R^2 and R^3 form a bond;

(ix) when Y represents N or N^+R^7 and R^2 is substituted by any of $NR^{10}R^{11}$, OR^{12} or F, then the substituent and the ring nitrogen of Y may not be attached to the same carbon atom of R^2;

(x) when R^7 is substituted by any of $NR^{16}R^{17}$, OR^{12} or halogen then the substituent and the ring nitrogen of Y may not be attached to the same carbon atom of R^7;

(xi) when one of B, D, E and G represents N, then X does not represent NR^4;

(xii) when Y represents CR^{18}, then X represents CR^3R^6;

with the further provisos that:

(a) when B, D, E and G all represent CH, X represents CHR^3, Y represents N, R^1 and R^5 form a bond, R^8 represents H and R^2 and R^3 together represent a bond, then Ar^1 does not represent unsubstituted phenyl, 4-chlorophenyl, 4-fluorophenyl or 4-methoxyphenyl;

(b) when B, D, E and G all represent CH, X represents CHR^3, Y represents N^+R^7, R^1 and R^5 form a bond, R^2 and R^3 represents a bond, R^8 represents H, and R^7 represents methyl, then Ar^1 does not represent unsubstituted phenyl;

(c) when B, D, E and G all represent CH, X represents CH_2, Y represents N, R^1 and R^5 form a bond, R^8 represents H, and R^2 represents isopropyl, then Ar^1 does not represent unsubstituted phenyl or 4-bromophenyl; and

(d) when B, D, E and G all represent CH, X and Y represent CH_2 and R^1 and R^5 form a bond, then Ar^1 does not represent unsubstituted phenyl.

or a pharmaceutically acceptable derivative thereof.

3. A compound of formula I as claimed in claim 1 or claim 2, wherein Ar^1 represents phenyl or pyridyl.

4. A compound of formula I as claimed in claim 3, wherein Ar^1 represents phenyl.

5. A compound of formula I as claimed in claim 3 or claim 4, wherein Ar^1 has a substituent in the *para* position.

6. A compound of formula I as claimed in claim 5, wherein Ar^1 has a Cl, Br, CF_3, C_2F_5, OCF_3 or SCH_3 substituent in the *para* position.

7. A compound of formula I as claimed in any preceding claim, wherein Y represents N^+R^7, and X represents CR^3R^6 in which R^3 forms a bond with R^2 and R^6 represents alkyl.

8. A compound of formula I as claimed in claim 7, wherein R^6 represents branched alkyl.

9. A compound of formula I as claimed in any one of claims 1 to 6, wherein X represents NR^4 in which R^4 represents a bond with R^2 and Y represent N^+R^7.

10. A compound of formula I as claimed in any preceding claim, wherein B represents CA.

11. A compound of formula I as claimed in claim 10, wherein A represents F.

12. A compound of formula I as claimed in any preceding claim, wherein D or G represents N.

13. A compound of formula I as claimed in any preceding claim, wherein R^1 represents a bond with R^2 or R^5.

14. A compound of formula I as claimed in claim 13, wherein R^1 represents a bond with R^5.

15. A compound according to claim 2 which is:
3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt,
2-(4-Trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-(4-Chlorophenyl)-2,5-dihydro-5-methyl-3*H*-pyrazolo[4,3-*c*]cinnolin-3-one,
2-(4-Chlorophenyl)-2,3a,4,5-tetrahydro-3a,4-dimethylpyrazolo[4,3-*c*]isoquinolin-3-one,
2-(4-Chlorophenyl)-3a,4-dihydro-3a,4-dimethyl-2*H*-pyrazolo[4,3-*c*]isoquinoline-3,5-dione,
2-(4-Chlorophenyl)-2,4-dihydro-3-hydroxy-4-methylpyrazolo[4,3-*c*]isoquinolin-5-one
3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-(3-quinolyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(3-Quinolyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-(3,4-Dichlorophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt,
2-(3,4-Dichlorophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-([1,1'-Biphenyl]-4-yl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-methylphenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt,
2-(4-Methylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-(4-Bromophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Bromophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-(3-Trifluoromethylphenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt,
2-(3-Trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-[4-(1,1-Dimethylethyl)phenyl]-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-(4-Trifluoromethoxyphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-(4-Chlorophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,

2-(4-Chlorophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]cinnolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-(3-quinolyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(6-Chloro-3-pyridyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(3,4-Dichlorophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-(4-methylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Bromophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-(3-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-[4-(1,1-Dimethylethyl)phenyl]-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(6-Chloro-3-pyridyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-(6-methyl-3-pyridyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-trifluoromethylphenyl)-3-hydroxy-4-(2-hydroxyethyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-(5-methyl-2-pyridyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-[4-(1-methylethyl)phenyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-(4-nitrophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Cyanophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Carboxyphenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,

2-(4-Chloro-3-trifluoromethylphenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt,
2-(4-Trifluoromethoxyphenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-(4-methylthiophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
4-Cyclopropyl-3-hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
4-Cyclopropyl-3-hydroxy-2-(6-methyl-3-pyridyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
4-[(1,1-Dimethyl-2-hydroxy)ethyl]-3-hydroxy-2-[(4-trifluoromethyl)phenyl]-2*H*-pyrazolo [4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-(2-methoxyethyl)-2-[(4-trifluoromethyl)phenyl]-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-3-hydroxy-4-[2-(methylthio)ethyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-[2-(methylthio)ethyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt,
4-Cyclopropyl-2-(4-trifluoromethoxyphenyl)-3-hydroxy-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chloro-3-trifluoromethylphenyl)-4-cyclopropyl-3-hydroxy-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt,
4-Cyclopropyl-3-hydroxy-2-(4-methylthiophenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-phenyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
4-Ethyl-3-Hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Trifluoromethylphenyl)-4-(1-ethoxycarbonylmethyl)-3-hydroxy-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-phenyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-(1-methylethyl)-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-(1-methylethyl)-2-(3-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,

3-Hydroxy-2-(4-iodophenyl)-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(6-Chloro-3-pyridyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-[4-(1-Methylethyl)phenyl]-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-(4-Pentafluoroethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2,4-Dihydro-3-hydroxy-4-methyl-2-(2-pyrimidinyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one,
2-([1,1'-biphenyl]-4-yl)-2,4-dihydro-3-hydroxy-4-methyl-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one,
2,4-Dihydro-3-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one,
2-(6-Chloro-3-pyridyl)-2,4-dihydro-3-hydroxy-4-methyl-5*H*-pyrazolo[4,3-*c*]isoquinolin--5-one,
2,4-Dihydro-3-hydroxy-2-(4-iodophenyl)-4-methyl-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one,
2,4-Dihydro-3-hydroxy-4-(4-methoxyphenylmethyl)-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one,
2,4-Dihydro-3-hydroxy-4-(1-methylethyl)-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo-[4,3-*c*]isoquinolin-5-one,
2,4-Dihydro-3-hydroxy-4-methyl-2-[4-(1-methylethyl)phenyl]-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one,
2,4-Dihydro-3-hydroxy-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinoli-5-one,
2,4-Dihydro-3-hydroxy-2-[4-(1-methylethyl)phenyl]-5*H*-pyrazolo[4,3-*c*]isoquinolin-5one,
2,4-Dihydro-3-hydroxy-2-([1,1'-biphenyl]-4-yl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one,
2-(4-Chlorophenyl)-3-hydroxy-4-[(4-methoxyphenyl)methyl]-5-methyl-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-5-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
4-Cyclopropyl-3-hydroxy-5-methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-(2-methoxyethyl)-5-methyl-2-[(4-trifluoromethyl)phenyl]-2*H*-pyrazolo [4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-3-hydroxy-4,5-dimethyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
5-Ethyl-3-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-5-methyl-4-(1-methylethyl)-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt,

4-Methyl-5-(1-methylethyl)-3-hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4,5-dimethyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
5-Chloro-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
3a,4-Dihydro-3a-hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin--3,5-dione,
2,4-Dihydro-3-methoxy-4-methyl-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinolin-5-one,
2-(4-Chlorophenyl)-4-{2-(*N*,*N*-dimethylamino)ethyl}-3-hydroxy-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-methyl-2-(4-methylsulfinylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-3-hydroxy-4-[2-(methylsulfinyl)ethyl]-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
3-Hydroxy-4-[2-(methylsulfinyl)ethyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
5-[2-(4-Methoxyphenyl)ethyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
9-Fluoro-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-7-fluoro-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
7-Fluoro-3-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-4-cyclopropyl-9-fluoro-3-hydroxy-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
4-Cyclopropyl-9-fluoro-3-hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-9-fluoro-3-hydroxy-4-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-9-fluoro-3-hydroxy-4-[(4-methoxyphenyl)methyl]-2*H*-pyrazolo-[4,3-*c*]isoquinolinium hydroxide, inner salt,
9-Fluoro-3-hydroxy-4-methyl-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-9-fluoro-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,

7-Fluoro-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-(4-Chlorophenyl)-7-fluoro-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
9-Fluoro-3-hydroxy-4-[(4-methoxyphenyl)methyl]-5-methyl-2-
-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Chlorophenyl)-9-fluoro-3-hydroxy-4-[(4-methoxyphenyl)methyl]-5-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
9-Fluoro-5-methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2-(4-chlorophenyl)-9-fluoro-5-methyl-2*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
2,4-Dihydro-3-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-5*H*-pyrazolo[4,3-*c*]isoquinoline-5-thione,
3-Hydroxy-4-methyl-5-methylthio-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide, inner salt,
2-(4-Trifluoromethylphenyl)-2,4-dihydro-5-imino-4-methyl-5*H*-pyrazolo[4,3-*c*]isoquinolin-3-ol,
3-Hydroxy-4-(4-methoxyphenyl)methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[3,4-*f*]-[1,7]naphthyridinium hydroxide, inner salt,
2-(4-Trifluoromethylphenyl)-2*H*-pyrazolo[3,4-*f*][1,7]naphthyridin-3-ol,
3-Hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[3,4-*f*][1,7]naphthyridinium hydroxide, inner salt,
2-(4-Chlorophenyl)-3-hydroxy-4-methyl-2*H*-pyrazolo[3,4-*f*][1,7]naphthyridinium hydroxide, inner salt,
3-Hydroxy-4-methyl-5-(dimethylamino)-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]-isoquinolinium hydroxide inner salt,
3-Hydroxy-4-methyl-5-morpholinyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide inner salt,
3-Hydroxy-4-methyl-5-piperazinyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide inner salt,
4,5-Dihydro-2-[4-(trifluoromethyl)phenyl]-2H-benz[g]indazol-3-ol,
4,5-Dihydro-2-(5-methyl-2-pyridinyl)-2H-benz[g]indazol-3-ol,
2-[4-(Trifluoromethyl)phenyl]-2H-benz[g]indazol-3-ol,
2-(5-Methyl-2-pyridinyl)-2H-benz[g]indazol-3-ol,
and pharmaceutically acceptable derivatives thereof.

15. A process for the preparation of compounds of formula I as defined in claim 1 or claim 2 which comprises:

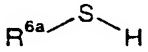
(a) preparation of compounds of formula I where X represents CH_2 or C=O, Y represents N, Z represents OR^8, R^5 and R^8 form a bond and R^1 and R^2 form a bond by oxidation of a corresponding compound of formula I where R^1 and R^2 both represent H, X, Y, Z and R^5 are as defined above and B, D, E, G and Ar^1 are as defined in claim 1;

(b) preparation of compounds of formula I where one of B, D, E and G represents CA wherein A represents amino by reduction of a corresponding compound of formula I, where one of B, D, E and G represents CA wherein A represents nitro and the remainder of B, D, E and G, and X, Y, Z, Ar^1, R^1, R^2 and R^5, are as defined in claim 1;

(c) preparation of compounds of formula I where one of B, D, E and G represents CA wherein A represents halo by diazotisation of a corresponding compound of formula I, where one of B, D, E and G represents CA wherein A represents amino and the remainder of B, D, E and G, and X, Y, Z, Ar^1, R^1, R^2 and R^5, are as defined in claim 1, and decomposition of the diazonium salt in the presence of the halide anion or a source thereof;

(d) preparation of compounds of formula I where one of B, D, E and G represents CA wherein A represents cyano by reaction of a corresponding compound of formula I, where one of B, D, E and G represents CA wherein A represents bromo and the remainder of B, D, E and G, and X, Y, Z, Ar^1, R^1, R^2 and R^5, are as defined in claim 1;

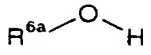
(e) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents alkylthio by displacement reaction of a corresponding compound of formula I, where X represents CR^3R^6 wherein R^6 represents methylthio or halogen, Y, Z, R^1, R^2, R^3 and R^5 are as defined above and B, D, E, G and Ar^1 are as defined in claim 1, with a compound of formula II:



(II)

wherein R^{6a} represents C_{1-6} alkyl;

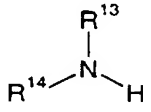
(f) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents alkoxy by displacement reaction of a corresponding compound of formula I, where X represents CR^3R^6 wherein R^6 represents methylthio or halogen, Y, Z, R^1, R^2, R^3 and R^5 are as defined above and B, D, E, G and Ar^1 are as defined in claim 1, with a compound of formula III:



(III)

wherein R^{6a} is as defined above;

(g) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents $NR^{13}R^{14}$ by displacement reaction of a corresponding compound of formula I, where X represents CR^3R^6 wherein R^6 represents methylthio or halogen, Y, Z, R^1, R^2, R^3 and R^5 are as defined above, and B, D, E, G Ar^1 are as defined in claim 1, with a compound of formula IV:



IV)

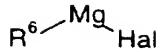
wherein R^{13} and R^{14} are as defined in claim 1;

(h) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents methylthio by reaction of a corresponding compound of formula I, where X represents C=S, Y represents N, Z represents OH, R^1, R^2, and R^5 are as defined above and B, D, E, G and Ar^1 are as defined in claim 1, with a methylating agent;

(i) preparation of compounds of formula I where X represents C=S, Y represents N, Z represents OH and R^1 represents a bond with R^5 by reaction of a corresponding compound of formula I, where X represents C=O, Y, Z, R^1, and R^5 are as defined above and B, D, E, G, Ar^1 and R^2 are as defined in claim 1, by thionation;

(j) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^- and R^6 represents halogen by reaction of a corresponding compound of formula I, where X represents C=O, Y represents N, Z represents OR^8, R^8 represents a bond with R^5 and B, D, E, G, Ar^1, R^1 and R^2 are as defined in claim 1, by halogenation;

(k) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents alkyl by reaction of a corresponding compound of formula I, where X represents C=O, Y represents N, Z represents OH, R^1 represents a bond with R^5, B, D, E, G, Ar^1 are as defined in claim 1 and R^2 represents a group corresponding to R^7 as defined in claim 1, by reaction with a nucleophilic alkylating reagent comprising a compound of formula V:



(V)

wherein R^6 is as defined above and Hal represents halogen, or another source of the anion corresponding to R^6;

(l) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents alkyl by reaction of a corresponding compound of formula I, where X represents CR^3R^6 wherein R^6 represents H, Y, Z, R^1, R^2, and R^5 are as defined above and B, D, E, G and Ar^1 are as defined in claim 1, with a nucleophilic alkylating reagent comprising a compound of formula V as defined, or another source of the anion corresponding to R^6;

(m) preparation of compounds of formula I where X represents C=O, Y represents N, Z represents OR^8, R^1 represents a bond with R^5, and R^8 represents alkyl by reaction of a corresponding compound of formula I, where Z represents OR^8 wherein R^8 represents H, X, Y, R^1, and R^5 are as defined above and B, D, E, G, Ar^1 and R^2 are as defined in claim 1, with a compound of formula VI:

R^8Hal (VI)

wherein R^8 represents alkyl and Hal is as defined above;

(n) preparation of compounds of formula I where R^1 represents OH, X represents C=O, Y represents N, Z represents OR^8 and R^5 represents a bond with R^8 by reaction of a corresponding compound of formula I, where Z represents O^-, R^1 and R^5 form a bond, X, Y, and R^2 are as defined above and B, D, E, G and Ar^1 are as defined in claim 1, by treatment with an oxidising agent;

(o) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond and R^1 and R^5 form a bond by reaction of a corresponding compound of formula I, where Y represents N, Z represents OH, X, R^1, R^2, and R^5 are as defined above and B, D, E, G and Ar^1 are as defined in claim 1, with a compound of formula IX:

R^7Hal (IX)

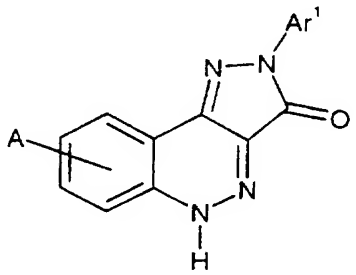
wherein R^7 is as defined in claim 1 and Hal are as defined:

(p) preparation of compounds of formula I where X represents C=O, R^2 does not represent H, Y represents N, Z represents OH and R^1 represents a bond with R^5 by reaction of a corresponding compound of formula I, where R^2 represents H, X, Y, Z, R^1 and R^5 are as defined above and B, D, E, G and Ar^1 are as defined in claim 1, with a compound of formula VII:

R^2Hal (VII)

wherein R^2, not representing H, is as defined in claim 1 and Hal is as defined above;

(q) preparation of compounds of formula I where B, D, E and G represent CH or CA, X represents NR^4, Y represents N^+R^7, Z represents O^-, R^4 and R^2 form a bond and R^1 and R^5 form a bond by reaction of a compound of formula VIII:



(VIII)

wherein A and Ar^1 are as defined in claim 1, with a compound of formula IX as defined above;

(r) preparation of compounds of formula I where B, D, E and G represent CH or CA, X represents NR^4, Y represents N, Z represents OR^8, R^2 and R^1 form a bond and R^5 and R^8 form a bond by reaction of a compound of formula VIII as defined above with a compound of formula X:

R^4Hal (X)

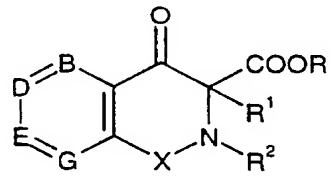
wherein R^4 is as defined in claim 1 and Hal is as defined above;

(s) preparation of compounds of formula I where X represents CR^3R^6, Y represents N, Z represents OH, R^3 and R^2 form a bond and R^1 represents a bond with R^5 by treatment of a corresponding compound of formula I, where Y represents N^+R^7, Z represents O^-, R^7 represents $CH_2C_6H_4Oalkyl$, X, R^1, R^2, and R^5 are as defined above, and B, D, E, G and Ar^1 are as defined in claim 1, with an acid;

(t) preparation of compounds of formula I where X represents CR^3R^6, Y represents N, Z represents OH, R^3 and R^2 form a bond and R^1 represents a bond with R^5 by treatment of a corresponding compound of formula I, where Y represents N^+R^7, Z represents O^-, R^7 represents CH_2phenyl (optionally substituted by C_{1-6} alkyl or C_{1-6} alkoxy), X, R^1, R^2, and R^5 are as defined above, and B, D, E, G and Ar^1 are as defined in claim 1, with hydrogen;

(u) preparation of compounds of formula I where X represents C=O, Y represents N, Z represents OH, R^2 represents H and R^1 represents a bond with R^5 by treatment of a corresponding compound of formula I, where Y represents N^+R^7, Z represents O^-, R^7 represents $CH_2C_6H_4O$alkyl, X, , R^1, R^2, and R^5 are as defined above, and B, D, E, G and Ar^1 are as defined in claim 1, with an acid;

(v) preparation of compounds of formula I where X represents CR^3R^6, Y represents N^+R^7, Z represents O^-, R^3 and R^2 form a bond, R^1 and R^5 form a bond and R^6 represents H by reaction of a compound of formula XI:



(XI)

where X represents CH_2, R^1 represents H, R^2 represents a group corresponding to R^7 as defined in claim 1 in the compound of formula I, B, D, E and G are as defined in claim 1 and R is alkyl, with a compound of formula XII:

$$Ar^1NHNH_2 \qquad \text{(XII)}$$

wherein Ar^1 is as defined in claim 1;

(w) preparation of compounds of formula I where X represents C=O, R^2 does not represent H, Y represents N, Z represents OH and R^1 represents a bond with R^5 by reaction of a compound of formula XI as defined above, where X represents C=O, R^1 represents H, R^2 is as defined above, R is as defined above and B, D, E and G are as defined in claim 1, with a compound of formula XII as defined above, wherein Ar^1 is as defined in claim 1;

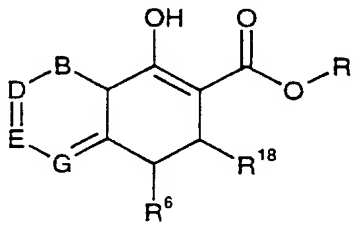
(x) preparation of compounds of formula I where X represents CH_2, Y represents N^+R^7, Z represents OR^8, R^8 and R^5 form a bond and R^1 represents alkyl by reaction of a compound of formula XI as defined above, where X represents CH_2, R^1 represents

alkyl, R is as defined above and B, D, E, G and R^2 are as defined in claim 1, with a compound of formula XII as defined above, wherein Ar^1 is as defined above;

(y) preparation of compounds of formula I where X represents C=O, Y represents N, Z represents OR^8, R^8 and R^5 form a bond and R^1 represents alkyl by reaction of a compound of formula XI as defined above, where X represents C=O, R^1 represents alkyl, R^2 represents H or alkyl, R is as defined above and B, D, E and G are as defined in claim 1, with a compound of formula XII as defined above, wherein Ar^1 is as defined above;

(z) preparation of compounds of formula I where X represents CR^3R^6, Y represents CR^{18}, Z represents OH, R^1 and R^5 form a bond and R^2 and R^3 form a bond by oxidation of a corresponding compound of formula I where X represents CR^3R^6, Y represents CR^{18}, Z represents OH, R^2 and R^3 represent H, R^1 and R^5 form a bond and B, D, E, G, Ar^1, R^6 and R^{18} are as defined in claim 1; or

(aa) preparation of compounds of formula I where X represents CR^3R^6, Y represents CR^{18}, Z represents OH, R^2 and R^3 represent H and R^1 and R^5 form a bond by reaction a compound of formula XII as defined above with a compound of formula XX:



(XX)

wherein R is as defined above and B, D, E, G, R^6 and R^{18} are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/00471

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 471/04, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9106298 A1 (PHARMACIA AB), 16 May 1991 (16.05.91) --	1-15
X	EP 0526840 A1 (KYOWA HAKKO KOGYO CO., LTD.), 10 February 1993 (10.02.93) --	1-15
X	Journal of heterocyclic chemistry, Volume 13, No 3, June 1976, Robert W. Hamilton, "The Antiarrhythmic and Antiinflammatory Activity of a Series of Tricyclic Pyrazoles" page 545 - page 553 --	1-15

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 1997	05 -07- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/00471

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	IL FARMACO, Volume 50, No 3, 1995, Silvia Schenone et al, "2-aryl-3-phenylamino-4, 5-dihydro-2H-benz(g)indazoles with antiarrhythmic and local anaesthetic activities" page 179 - page 182 --	1-15
A	GB 2166439 A (SHIONOGI SEIYAKU KABUSHIKI KAISHA), 8 May 1986 (08.05.86) --	1-15
A	GB 2131801 A (CIBA-GEIGY AG), 27 June 1984 (27.06.84) -- --------	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/00471

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-15
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see annexed sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

The formulation of the claims is so complicated, owing to the very wide range of combinations of variable parts and disclaimer parts, that PCT Article 6 is no longer complied with. This Article specifies that the claims must be formulated in a clear and concise manner. The search has therefore been limited to compounds with the same or similar structure having the same or similar effects.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/06/97

International application No.
PCT/SE 97/00471

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9106298 A1	16/05/91	SE 8903564 D	00/00/00
EP 0526840 A1	10/02/93	CA 2074876 A	01/02/93
		JP 5194515 A	03/08/93
		US 5281610 A	25/01/94
GB 2166439 A	08/05/86	CA 1269983 A	05/06/90
		EP 0182165 A,B	28/05/86
		SE 0182165 T3	
		JP 1702666 C	14/10/92
		JP 3070706 B	08/11/91
		JP 61112075 A	30/05/86
		US 4690930 A	01/09/87
GB 2131801 A	27/06/84	BE 898383 A	06/06/84
		CH 656127 A,B	13/06/86
		DE 3343922 A	28/06/84
		FR 2537584 A,B	15/06/84
		JP 59110694 A	26/06/84
		NL 8304224 A	02/07/84
		US 4524146 A	18/06/85